American Heart Journal

Vol. 29 April, 1945 No. 4

In Memoriam

THOMAS LEWIS

1881-1945

The world has lost a great medical leader. Thomas Lewis died at his home in Rickmansworth, England, on March 17, 1945, in his sixty-fourth year, after a fourth attack of myocardial infarction, the first illness of the sort having occurred eighteen years earlier. Like his own master, James Mackenzie, he suffered from a disease of the circulation, but despite it, made some of his most important contributions after the onset of this trouble.

Thomas Lewis was born in Wales in 1881, the son of Henry Lewis of Cardiff. He received his collegiate and professional education at the University College of Cardiff and the University College Hospital Medical School of London, where later he served as physician and investigator. He worked for years as a Beit Memorial Fellow in his animal and clinical investigations and as a member of the Medical Research Council from 1933 to 1937. He was consultant to the City of London Hospital, the Eastern Command, and the Ministry of Pensions, and, at one time (in 1914), when the present writer was working under his direction, he served as medical consultant to the London Zoo, where he was able to secure all kinds of hearts of interest. He gave various notable lectures, including the Oliver-Sharpey, the Linacre, the Harvey and the Herter Lectures in 1914, the Croonian of the Royal Society in 1917, the Royal Medical in 1927, the St. Cyres and Wesley M. Carpenter Lectures in 1931, the Mary Scott Newbold in 1932, the Harveian Oration in 1933, the Huxley Lecture in 1935, and the George Halliburton Hume in 1937. Many honors came to him: C.B.E. in 1920, knighthood in 1921, D.Sc., LL.D., the Royal Medal in 1927, the Copley medal of the Royal Society in 1941, and the Conway Evans Prize in 1944, the last having been presented to him but a few months before his death.

He married Lorna, daughter of Frank Trehorne James of Merthyr Tydfil, Wales, in 1916. Their three children are Patricia, Christopher (studying medicine at Oxford), and Philippa, who, because of her tender age, spent four years (1940 to 1944) in this country.

Sir Thomas was always greatly interested in natural history and spent many hours throughout his life studying and photographing birds in their natural surroundings. It had been a hope of his some day to publish his rare collection of bird pictures.

Although it has always been hard to classify Thomas Lewis, his chief contributions were the links he created between physiological knowledge and technique and the medical clinic. Thus he was one of the pioneers in sound clinical investigation, a physiologist in the clinic and a clinician in the laboratory of animal experimentation.

Painstaking, accurate, and indefatigable observation of the processes

of physiology, normal and abnormal, in animals and in man, helped by the application of the experimental method, was the keynote of Thomas Lewis' scientific life. It happened through Mackenzie's influence that the circulatory system was his special field of interest, but he preached the gospel of his high standards of scientific endeavor to all workers in clinical medicine in order to raise up a group of vigorous investigators in what he called clinical science. He passed on the torch which he had carried for years, beginning in 1909, the date of the first issue of the journal *Heart,* to the editors of *Clinical Science* (incorporating *Heart*) in 1933. His emphasis was on the study of man himself.

In the course of his studies he made many contributions of value and several of lasting note. He described auricular fibrillation in man in 1909, the spread of the electrical impulse in the mammalian heart over a period of a number of years following that date, the characteristics of the various arrhythmias and their responses to various drugs, peripheral vascular disorders, the reactions of the blood vessels of the skin, and the mechanism of pain. He wrote important books at a young age, his most notable being his masterpiece, the *Mechanism of the Heart Beat,* in 1911, when he was only 29. This volume he enlarged considerably in two later editions which he called *The Mechanism and Graphic Registration of the Heart Beat,* the third being published in 1925. He wrote voluminously but always to the point without waste of words.

Among his other more important books were those on *The Soldier's Heart and the Effort Syndrome* (first edition, 1918, second edition, 1940), *Blood Vessels of the Human Skin and Their Responses* (1927), *Vascular Disorders of the Limbs* (1936), and *Pain* (1942). He assembled his experience and ideas about *Heart Disease* in a small volume in 1932 (second edition, 1937) and he prepared small guidebooks for the clinician, summarizing the current knowledge of the arrhythmias assembled by Mackenzie, Wenckebach, himself, and others, entitled *Clinical Disorders of the Heart Beat* (first edition, 1912; sixth edition, 1926), and of electrocardiography in the early days entitled *Clinical Electrocardiography* (first edition, 1913; sixth edition, 1937). *Lectures on the Heart,* published in 1915, comprised the series of special talks that he gave in the United States on one of his visits to this country.

But more important than his writings was his influence on his students and associates and on the medical thought of his time. His was a forceful, keen intellect, brooking no deceit, laziness, or sluggish inaccurate thinking or writing. He was very economical in his own speech and intolerant of verbosity in others. His thoughts usually leaped ahead of those of the people about him, and in his earlier years he expressed his impatience often forcefully—it was a waste of his valuable time, he seemed to imply, to have to explain things over and over. As he grew older he became more tolerant of the shortcomings of others and of the contributions that others were making, but his earlier attitude was a powerful stimulus to those of his students who could weather the strain, to emulate his industry, initiative, and accuracy.

Among his many students were young American physicians who, at the present day, may be found in the larger medical centers of this country at the peaks of their useful careers in medicine, particularly in their chosen field of cardiology, and who gratefully acknowledge the debt they owe to the great master. It is therefore particularly appropriate for the American Heart Association through its JOURNAL to render herewith its homage to the memory of Thomas Lewis.

PAUL D. WHITE.

Original Communications

MANAGEMENT OF THE MYXEDEMATOUS PATIENT WITH SYMPTOMS OF CARDIOVASCULAR DISEASE

THOMAS HODGE MCGAVACK, M.D., KURT LANGE, M.D., AND DAVID SCHWIMMER, M.D.
NEW YORK, N. Y.

THAT cardiac complications are frequent in myxedema is proved by the fact that twenty-four patients with frank myxedema and cardiac complaints have been seen on the wards of a general city hospital within a period of four years. Nineteen (79 per cent) of these were admitted because of the severe cardiac condition, with either right or left ventricular failure, or both. Eight (42 per cent) of these nineteen died. Five died without receiving any thyroid medication, and despite energetic cardiac treatment. Three of these were in the hospital less than forty-eight hours. The other two lived twenty-one and forty-one days, respectively. We believe the status of these patients could have been materially improved by the judicious use of thyroid therapy. On the other hand, it appears that, in two of the three cases in which thyroid hormone was given, its overzealous administration resulted in death.

In ten of the nineteen cases we were able to make serial studies of the basal metabolic rate, the blood cholesterol, the blood proteins, the circulation time, capillary permeability, electrocardiograms, and teleroentgenograms. Out of these observations have come data which may establish useful criteria for following therapy.

METHODS

All patients remained in the hospital for the entire period of study. All laboratory methods were those in common clinical use, with the following exceptions: Cephalin flocculation tests were done by the method originally described by Hanger,[1] using cephalin prepared according to the method of Thudichum;[2] fresh reagent was prepared once weekly, as suggested by others.[3] Drekter's method[4] was used for estimating blood cholesterol; normal levels by this method range from 130 to 200 mg. per 100 c.c., with the free fraction not exceeding 35 per cent of the total. Circulation time and capillary permeability were ascertained

From the Department of Medicine, New York Medical College, and the Research Unit of Metropolitan Hospital, New York City.
Read before a scientific session of the New York Heart Association, May 2, 1944.
Aided by a grant from the John and Mary R. Markle Foundation.
Received for publication June 21, 1944.

TABLE I

CARDIAC ABNORMALITIES OF NINETEEN PATIENTS WITH MYXEDEMA

CASE*	DIAGNOSIS				HEART SIZE ROENTGENOGRAM
	ETIOLOGICAL†	ANATOMIC	PHYSIOLOGIC‡	FUNCTIONAL§	
1	Arteriosclerosis Hypertension	Coronary sclerosis Hypertrophy and dilatation	First degree A-V block; left bundle branch block; low voltage	Right and left failure—IV	L
3	Hypertension	Hypertrophy and dilatation	Abnormal T waves	Right failure—III	N
4	Arteriosclerosis Hypertension	Hydropericardium Hypertrophy and dilatation Aortic insufficiency		Right and left failure—IV	--
5	Arteriosclerosis	Coronary thrombosis	Right bundle branch block; low voltage	Right and left failure—IV	L
6	Arteriosclerosis Hypertension	Coronary sclerosis	Widened QRS complexes; left ventricular strain; low voltage	Left failure—IV	L
8	----------	Enlargement with mitralization	Prolonged A-V conduction; low voltage	Angina of effort—III	L
9	----------	Enlargement	Bradycardia; low voltage	Angina of effort—II	L
11	Arteriosclerosis	Hypertrophy and dilatation	Abnormal T waves; low voltage	Left failure—III	L
12	----------	Enlargement	Bradycardia	Angina of effort—II	L
14	Arteriosclerosis	Enlargement Coronary sclerosis	Multiple auricular extrasystoles; abnormal T waves; low voltage	Left Failure—IV	L
15	Syphilis Hypertension	Aortitis with aortic insufficiency; hypertrophy left ventricle	Left ventricular strain; low T waves	Angina of effort	L
16	Arteriosclerosis	Coronary thrombosis	----------	Right and left failure—IV	L
17	Arteriosclerosis	Hypertrophy and dilatation; coronary sclerosis	Intraventricular block; auricular fibrillation; low voltage	Right and left failure—IV	L
19	Thrombosis pulmonary artery	Hypertrophy and dilatation	Prolonged A-V conduction; low S-T segment; low voltage	Right and left failure—IV	L
20	Diabetes mellitus; arteriosclerosis	Hypertrophy and dilatation; coronary thrombosis	Ventricular extrasystoles; low T waves; low voltage	Right and left failure—IV	L
21	Hypertension Arteriosclerosis	Coronary sclerosis	Left ventricular strain	Left failure—III	L
22	----------	----------	Low voltage	Angina of effort—III	L
23	Hypertension Arteriosclerosis	Hydropericardium	Intraventricular block; low voltage	Right and left failure—IV	L
24	Arteriosclerosis	Hypertrophy and dilatation; coronary sclerosis	Low voltage	Right and left failure—IV	L

*Omitted numbers represent cases in the series which showed minimal or insignificant changes. They will be dealt with elsewhere (see reference 12).

†Myxedema is understood to play a causative role in each instance.

‡This includes important electrocardiographic findings.

§Roman numerals refer to the classification of the American Heart Association.

‖L = large.
N = within normal limits.

by the fluorescein technique of Lange, et al.[5, 6] Any modification of other procedures was chiefly concerned with the methods of taking specimens and the amounts of serum used, as described elsewhere.[7]

INITIAL OBSERVATIONS

The clinical picture of myxedema was present in twenty-four patients, of whom nineteen had cardiac complications.

1. *The cardiac condition* was believed to be due solely to the myxedema in four cases (Table I). Myxedema undoubtedly played a role in every case, but other etiological factors could not be excluded. That is, one patient had syphilitic aortitis; thirteen, arteriosclerotic changes; and five, hypertension with cardiac involvement. Five electrocardiograms revealed changes caused by myxedematous involvement only; nine showed such changes superimposed upon other types of involvement; and, in six, no such alterations could be observed. Myxedema alone produced cardiac enlargement in two instances; in neither of these was pericardial fluid present. The enlargement was associated with hypertension in three cases, and with right and/or left ventricular failure in thirteen cases.

2. *The basal metabolic rate* was measured in nineteen cases (Table II). The lowest rate was –46 (Case 9, R. W.), and the highest, –10 (Case 17, K. B.), with a general average of –25.5 per cent. In seven cases the basal metabolic rate on, or shortly after, admission was obviously elevated as a result of the cardiac condition. Four of these were among the patients with basal metabolic rates between –10 and –19 per cent, and the remainder fell into the group with values between –20 and –29 per cent.

TABLE II

DATA FROM INITIAL OBSERVATIONS ON TWENTY-FOUR PATIENTS WITH MYXEDEMA
(Male, four; female, twenty)
Basal metabolic rate* (nineteen patients)
Low = -46; High = -10; Average = -25.5

RANGE OF VALUES	NUMBER OF CASES
Between -10 and -19	7
Between -20 and -29	8
Between -30 and -39	3
Between -40 and -49	1

Values in percentage.
*Basal Metabolic rate probably influenced by cardiac condition in seven cases, of which four were in the group with rates below –20 per cent.

3. The highest *blood cholesterol* (Table III) was 750 mg. per 100 c.c., which occurred in a 71-year-old patient (Case 5, S. S.) who was admitted to the hospital because of dizziness, attacks of unconsciousness ("fits"), and shortness of breath. Her basal metabolic rate was –22 per cent. The lowest blood cholesterol was 112 mg. per 100 c.c.; this was observed in a 60-year-old woman whose cardiac failure was severe,

and whose myxedema was very slight (Case 17, K. B.). Her basal metabolic rate was only −10 per cent. However, her symptoms, signs, and course subsequent to the relief of the cardiac failure fully justified a diagnosis of myxedema, rather than one of simple hypothyroidism. The average blood cholesterol in eighteen cases shortly after admission was 364.3 mg. per 100 cubic centimeters. One of four patients whose cholesterol level was below 200 mg. per 100 c.c. had congenital myxedema, with patency of the ductus arteriosus and other anomalies. He died at the age of 9 months.

TABLE III

DATA FROM INITIAL OBSERVATIONS ON TWENTY-FOUR PATIENTS WITH MYXEDEMA
Blood Cholesterol* (eighteen patients)
Low = 112; High = 750; Average = 364.3

RANGE OF VALUES	NUMBER OF CASES
Below 200	4
Between 201 and 300	5
Between 301 and 400	4
Between 401 and 500	1
Between 501 and 600	2
Above 600	2

*In milligrams per 100 cubic centimeters.

4. Total *blood proteins* and the albumin, globulin, and fibrinogen fractions were ascertained in sixteen cases (Table IV). The highest figure for total protein was 10.52 Gm. per 100 c.c.; the lowest, 6.58; and the average, 8.28. In no instance was the albumin-globulin ratio reversed, but it approached 1 in three cases. Two of these had severe congestive failure at the time the specimens were taken. The third, our oldest patient, aged 71 years (Case 5, S. S.), was severely myxedematous and showed a moderate, anginal type of failure, but no congestive phenomena.

TABLE IV

DATA FROM INITIAL OBSERVATIONS ON TWENTY-FOUR PATIENTS WITH MYXEDEMA
Blood protein* (sixteen patients)
Low = 6.58; High = 10.52; Average = 8.28

RANGE OF VALUES	NUMBER OF CASES
Between 6.5 and 7.5	6
Between 7.6 and 8.0	5
Between 8.1 and 9.0	3
Above 9.0	2

*In percentage.

5. The *circulation time* on, or shortly after, admission, measured by a method previously described by one of us (K. L.[5]), averaged 23.3 seconds in thirteen cases (high normal, 17.5 seconds), with a low of 16 seconds and a high of 31 seconds.

6. *Capillary permeability*, as ascertained by the method of Lange, et al.,[5, 6] was increased in each of the eight cases in which it was studied

before treatment; the degree of change in one instance reached approximately 165 per cent above the average normal figure, and approximately 130 per cent above the upper normal limit (Fig. 1, tracing of G. F.). Unlike the circulation times and basal metabolic rates, these figures were not appreciably disturbed by cardiac edema, which has been previously shown not to influence capillary permeability.[8]

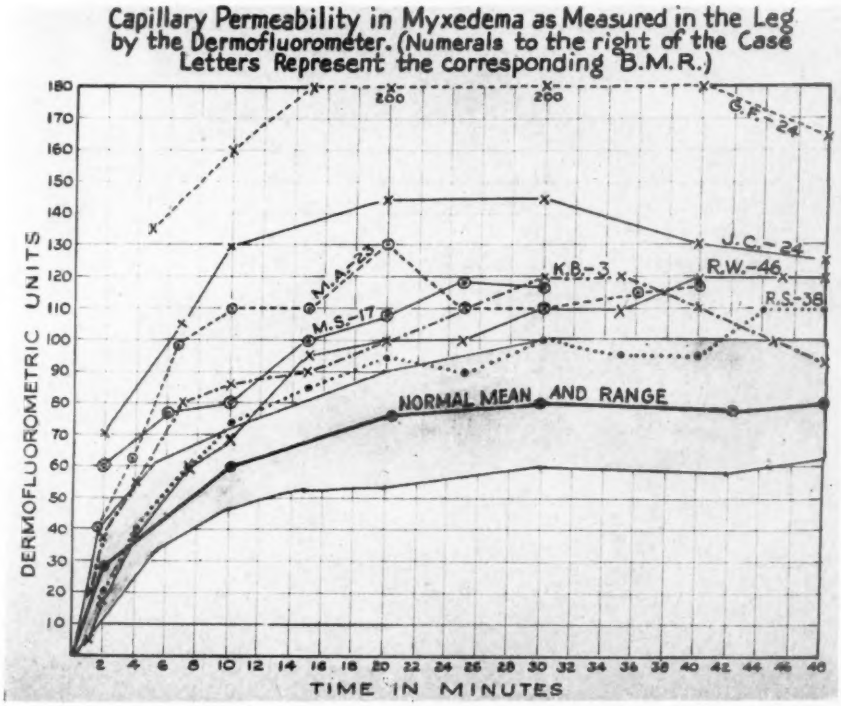


Fig. 1.

7. *Electrocardiograms* were taken on eighteen of the nineteen patients who showed signs of cardiac failure. Thirteen revealed low voltage in all leads and all complexes, and two of these showed no other electrocardiographic evidence of myocardial disturbance.

8. *Roentgenologic examination* of the heart and lungs was carried out on eighteen of the nineteen patients with cardiac failure. In eighteen cases the cardiothoracic ratio exceeded 0.50, and such patients are noted in Table I as having large hearts. Hydropericardium probably accounted for the entire enlargement in one case (Case 23, G. R.), and was diagnosed by physical examination, with subsequent confirmatory tap, in the one case in which roentgenographic study was not performed. In the four cases in which no cause for the cardiac condition other than the myxedematous state could be found, the enlarge-

ment of the heart was moderate, with the cardiothoracic ratio just above the upper normal limit (0.51) in one (Case 9, R. W.).

SUBSEQUENT DATA AND DISCUSSION

1. In cases of uncomplicated myxedema, a slow, uniformly steady loss of weight was a good index to the effectiveness of therapy, but afforded no help whatsoever when cardiac complications associated with congestive failure existed. Equally unreliable in the latter circumstances were the pulse rate and blood pressure.

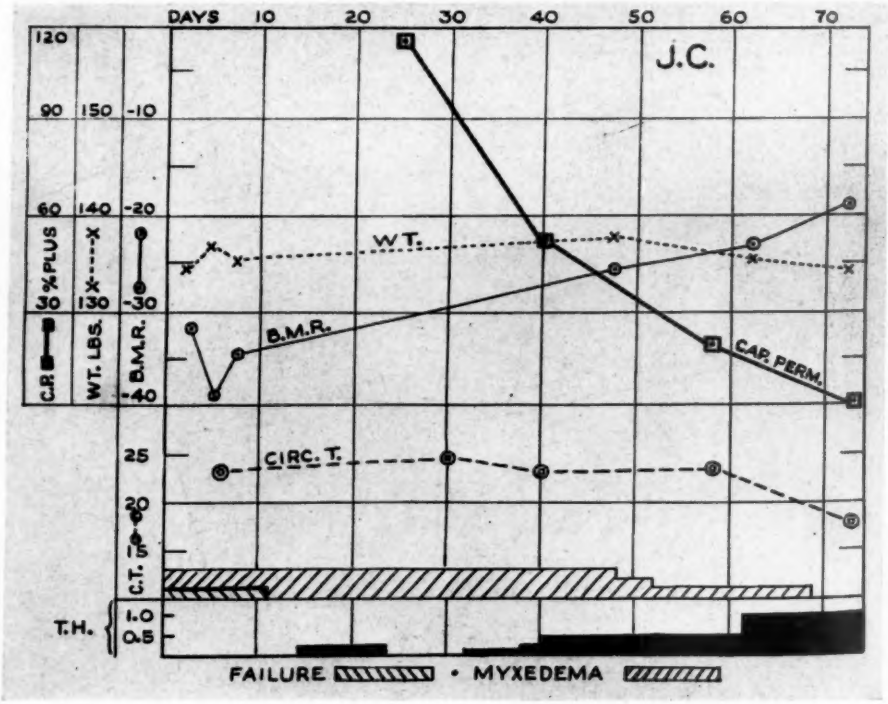


Fig. 2.—Case 8, J. C. Clinical chart. Note the early change in capillary permeability, the gradually rising basal metabolic rate, and the uninformative circulation time.

2. As a result of cardiac failure, the basal metabolic rate was uninformative in at least seven cases at a time when it was important to know whether or not the correct amount of desiccated thyroid substance was being used. The influence of cardiac failure alone is well illustrated in Figs. 2 and 3. In Case 8, J. C. (Fig. 2), the basal metabolic rate decreased from –32 to –39 per cent in three days as a result of improvement in the cardiac status. In Case 16, G. F. (Fig. 3), the rate rose from –24 to –13 per cent in nine days as a result of congestive failure, and fell to –42 per cent as soon as all the cardiac symptoms were controlled and before thyroid medication was begun.

Changes in the basal metabolic rate in cardiac disease have not been satisfactorily explained. At least two factors may alter the basal metabolic rate in cardiac failure. Dyspnea increases muscular effort and, therefore, the oxygen consumption. Edema increases weight and, therefore, lowers the calculated basal metabolic rate. However, the influence of the first of these two opposing mechanisms usually outweighs the second, so that the net result is usually a more or less marked elevation of the metabolic rate.

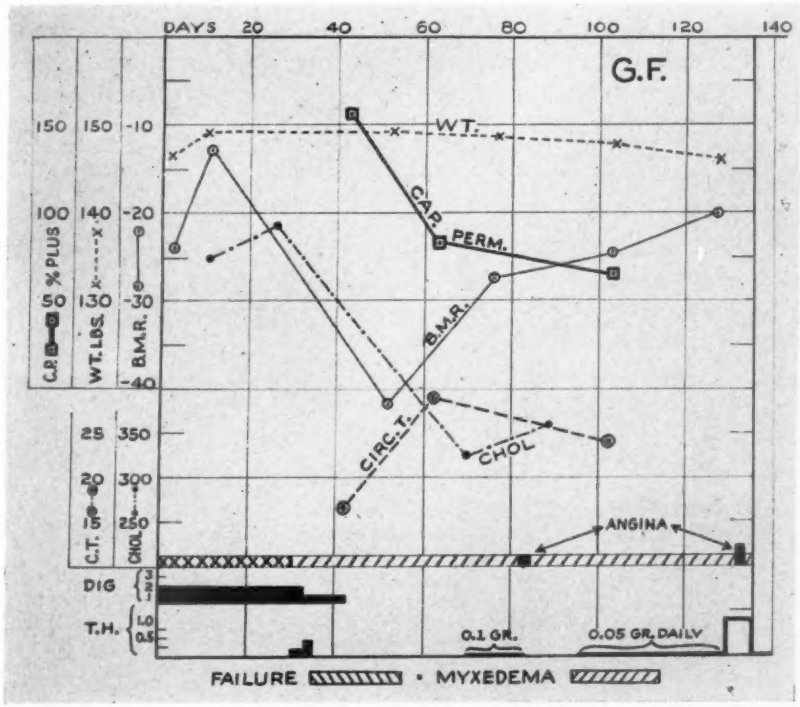


Fig. 3.—Case 16, G. F. Clinical chart. Note the false basal metabolic rate as a result of cardiac failure, with true figure about the fortieth day of observation. Capillary permeability was altered toward normal, along with cholesterol and the basal metabolic rate.

3. Values for total cholesterol were highly informative in confirming the presence of myxedema; normal levels were found in only four of twenty-four cases. Except in longstanding right-sided heart failure, the ratio of cholesterol in the free and combined forms was invariably within normal limits, whether the patient was in a myxedematous state, in cardiac failure, or normally controlled. When levels were originally high while myxedema existed, subsequent variations were always influenced by the degree of thyroid sufficiency; the value decreased with every increase in the basal metabolic rate, and in all instances attained normal levels when the patient's thyroid status was fully restored to normal. Similar variations occurred in patients with initially normal

figures, although the changes might not be sufficiently great to aid in the direction of therapy. In general, the cholesterol levels responded more slowly and more irregularly than did the basal metabolic rate in the patient without heart failure. In the latter state they were a reasonably reliable guide to the patient's thyroid status. For instance, the initial cholesterol level in Case 24 (M. F.) was 340 mg. per 100 c.c. of blood. When her myxedematous state was under satisfactory control, the cholesterol value was never observed to be greater than 200 mg. per 100 cubic centimeters. Conversely, it was never below that figure when any signs of hypothyroidism were present. Moreover, when she was myxedematous without cardiac failure, the levels were approximately the same as when the cardiac symptoms were in evidence. In

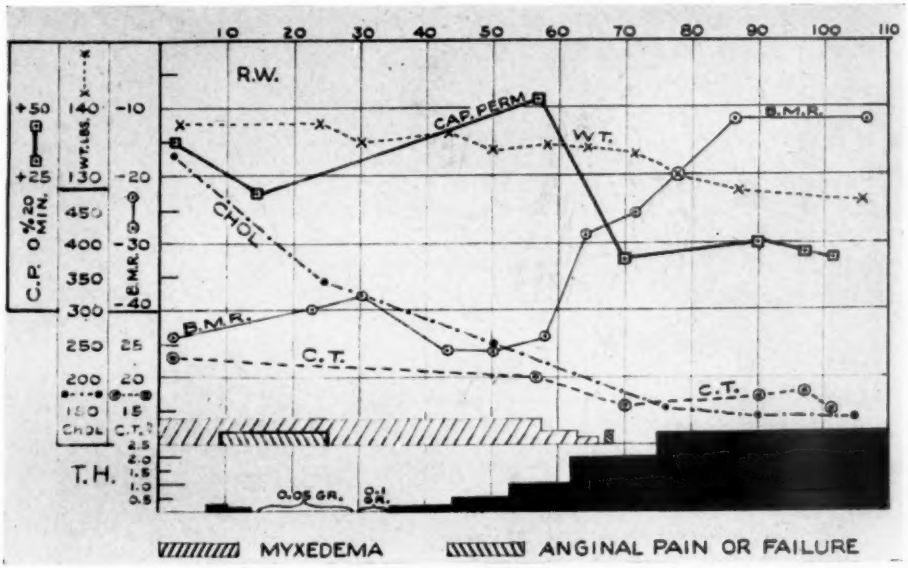


Fig. 4.—Case 9, R. W. Clinical chart. This record shows the response in a case of myxedema in which severe signs of failure never occurred.

other words, the total value seemed to be independent of her cardiac status, although the percentage of esters might be adversely influenced thereby. The change in cholesterol toward normal is of much more significance than the absolute level itself. This is illustrated in Case 16 (Fig. 3), in which the cholesterol level fell 260 mg. per 100 c.c. of blood between the twenty-sixth and seventieth days of observation, with simultaneous, favorable changes in basal metabolic rate and capillary permeability. The resulting level was still high (380 mg. per 100 c.c.), and the patient still had severe hypothyroidism, but was definitely improved. In Case 9 (R. W.) the changes were equally dramatic; normal levels were not reached until capillary permeability was normal and the basal metabolism had markedly improved (Fig. 4).

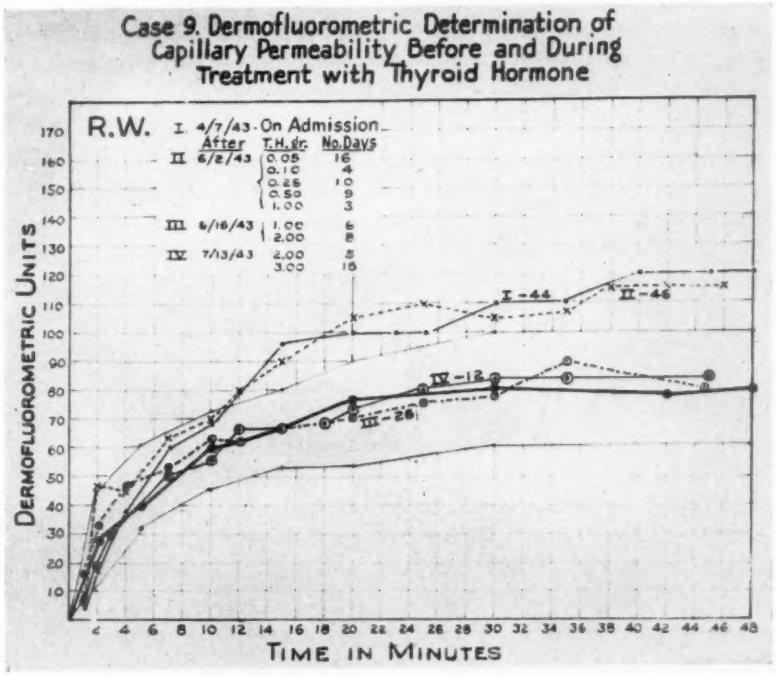


Fig. 5.

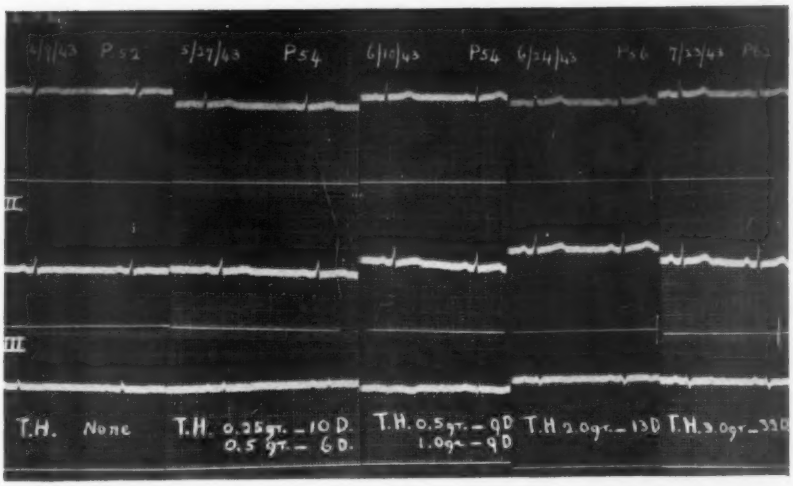


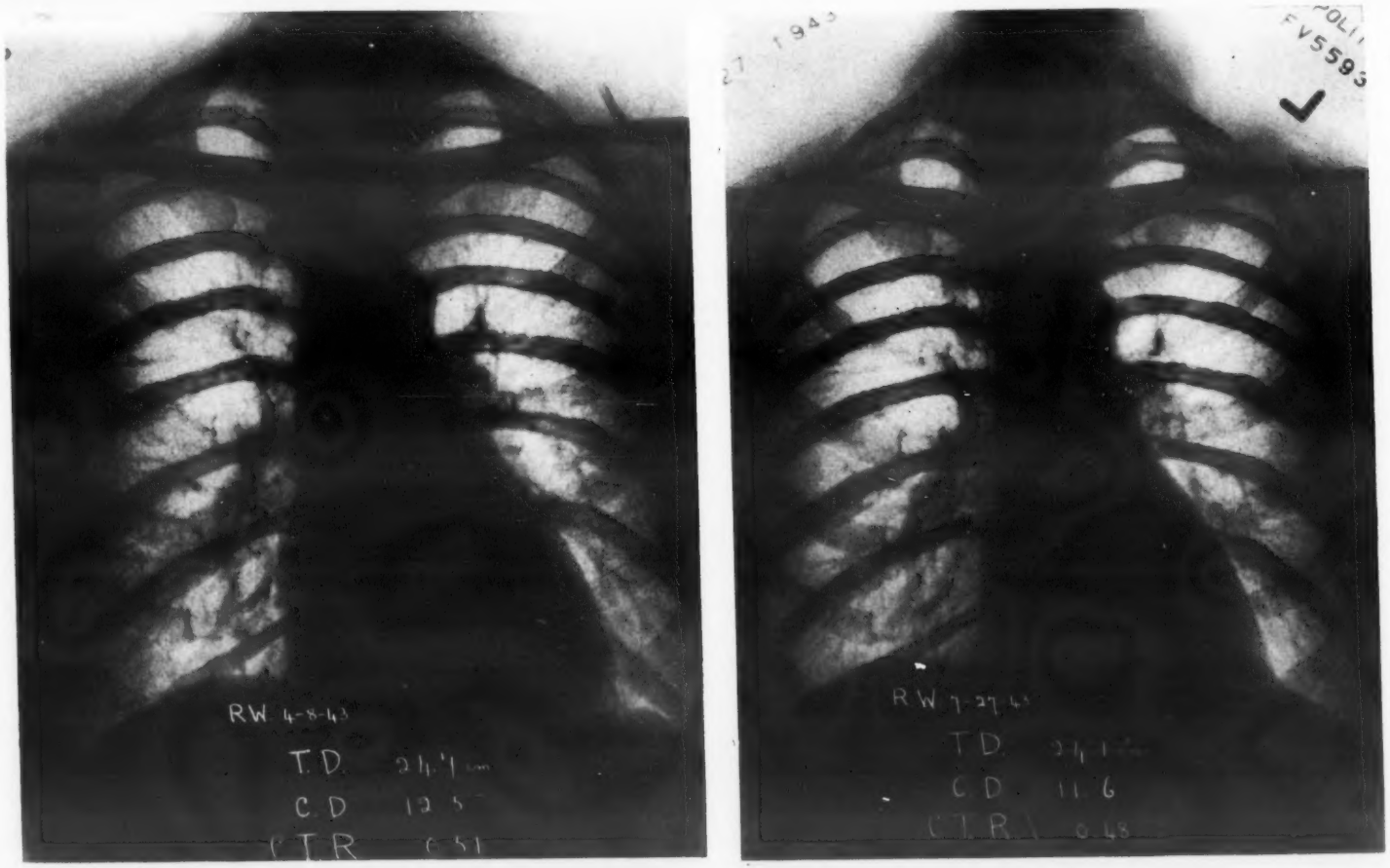
Fig. 6.—Electrocardiograms in Case 9, R. W. April 9, 1943, bradycardia and low voltage in all complexes. May 27, 1943, after a total of 5.5 grains desiccated thyroid substance taken in sixteen days without appreciable change. June 10, 1943, eighteen days later, during which 13.5 grains thyroid hormone were taken. Note increased amplitude of all complexes; T_2 still very low. Capillary permeability still high. June 24, 1943, T_2 greater than 1 mm.; capillary permeability normal. Basal metabolic rate still low, –26 per cent. July 23, 1943, patient clinically well; basal metabolic rate, –12; and capillary permeability normal.

4. If the figures for total blood proteins were above normal, they were of confirmatory value in establishing the diagnosis of myxedema. However, 36 per cent were well within normal range, and an additional 31 per cent could be looked upon as high normals (Table IV). Neither the total figure nor any fraction thereof was of any value in following the progress of the patient. The albumin-globulin ratio was equally uninformative. Under treatment with thyroid substance, high values were brought within the normal range, but the degree of change never reflected the patient's general condition, nor did it indicate thyroid status at any particular moment. In the interests of simplicity, serial figures for proteins have, therefore, been omitted from all of the graphs.

5. In the presence of both myxedema and cardiac failure, the circulation time is a totally unreliable method of gauging the progress or course of either. Of the two conditions, congestive failure has a more profound effect in raising the circulation time than does myxedema. The most marked increases were noted when both were present simultaneously. Case 8 (Fig. 2) illustrates the difficulty encountered in evaluating this test. The circulation time remained at a constantly high level until convalescence was well established.

6. Capillary permeability cannot be quantitatively measured in the Negro race, but in the white patient it has afforded one of the earliest and most reliable signs of diminution of the myxedema. It has been followed for periods of two to ten months in five cases. The records of some of these are shown graphically in Figs. 2 to 5, inclusive. The profound increase observed in myxedema shows improvement before it has been indicated by any other objective measure we have used. This test has the distinct advantage of being uninfluenced by cardiac decompensation.[8] The fluctuations in permeability are, moreover, quantitatively large (Figs. 2, 4, and 5), so that relatively slight improvement in the general condition of the patient is reflected in the curves obtained.

7. Electrocardiograms that showed changes due only to the myxedematous state were present in three of the nineteen patients who entered the hospital primarily because of the cardiac disturbance. In these, serial examinations showed a return to normal as the myxedema was relieved. In the serial tracings of R. W. (Case 8, Fig. 6), the bradycardia and the low voltage originally present in all complexes of all leads gave way gradually to a normal electrocardiogram as the myxedematous state disappeared under steadily increasing doses of thyroid hormone. The relationship of these cardiac changes to the other clinical data is readily appreciated by referring to Fig. 4, the "first day" of which is April 7, 1943. On the seventieth day of observation, June 16, 1943, the basal metabolic rate was rising, but was still far from normal (–26 per cent); the circulation time was for the first time within normal limits (16 seconds); the capillary permeability was normal; and the blood cholesterol several days later was 150 mg. per



A. *B.*

Fig. 7.—Case 9, R. W. Roentgenograms of the heart at 2 m., *A*, before treatment, and *B*, after treatment. Relatively uncomplicated myxedema enlarges the heart, an effect which thyroid hormone specifically abolishes.

100 cubic centimeters. Complete disappearance of the abnormal electrocardiographic features occurred between June 10, 1943, and June 24, 1943. That capillary permeability simultaneously decreased to slightly below the average normal mean, despite the continuation of a slow pulse rate and a low basal metabolic rate, would appear to be more than coincidental. It leads us to believe that changes in the capillary permeability of the cardiac musculature may have something to do with the low voltage which is usually present in cases of uncomplicated myxedema. Just what disturbances of water and electrolytic balance accompany this altered capillary state it is at present difficult to say. In any event, they seem to be capable of materially decreasing the functional capacity of the heart in such a manner as to lower its tolerance for thyroid hormone. Gradual improvement in the electrocardiogram and normalization of the capillary permeability curves appear to be satisfactory and safe guides for the administration of thyroid hormone to the myxedematous patient with cardiac failure, for their change toward the normal apparently goes hand in hand with a restoration of electrolytic, water, and nutritional balance within the tissues themselves.

8. Cardiac enlargement in the patient with myxedema uncomplicated by congestive failure or hypertension was rarely observed in the group of cases here studied. However, serial examinations in Case 9, R. W., afforded a comparison of the size of the cardiac silhouette before and after treatment. This patient had myxedema of severe degree and long standing which was complicated only by mild angina of effort. The size of the heart, therefore, would be expected to reflect only changes secondary to the myxedematous state. On admission, slight enlargement was noted (Fig. 7, *A*), with a cardiothoracic ratio of 0.51. Just prior to discharge, one hundred seven days later, after adequate thyroid therapy, the cardiothoracic ratio was 0.48, with a frontal cardiac area of normal proportions (Fig. 7, *B*). The improvement appeared concomitantly with stabilization of the patient's condition clinically and a return to normal of the other laboratory data. There is much dispute as to the nature of the cardiac enlargement in uncomplicated myxedema, but LaDue[9] has critically analyzed the problem in connection with a pathologic study of a patient who died with a "myxedema heart." Histologically, the lesions were not distinguishable from those of several other conditions, but, therapeutically, changes in cardiac function in myxedema responded quite specifically to thyroid hormone. The slight enlargement detectable roentgenographically would appear to be due to the interstitial edema that has now been described by several investigators.[9-11, 13] This concept receives support from the simultaneous disappearance of the abnormal changes in capillary permeability, the electrocardiogram, and the cardiac silhouette of the patient whose data we have just presented.

9. Therapy. The ill effects of initially high doses of thyroid (i.e., more than 0.5 grain daily) are illustrated nicely in Cases 1, 8, 9, 11, 12,

16, 22, and 24. In two instances (Cases 8 and 9) the dose had to be adjusted at levels as low as 0.05 grain daily before cardiac distress could be avoided.

In every case, from the standpoint of treatment, the cardiac disturbance was given precedence over the hypothyroidism, but the patient's condition was never fully satisfactory until both were treated. The unfavorable influence of the hypothyroid state upon cardiac function is well illustrated in Case 24 (M. F.). This patient, on the three hundred sixty-seventh day of observation, was taken off her previously satisfactory regime of 3 grains of digitalis daily and 1 grain of desiccated thyroid substance daily. Signs of myxedema were marked about sixty days later, but no evidence of cardiac failure appeared until two weeks after the myxedematous state had been established. It would appear from this and other observations that we cannot improve the cardiac status by completely withholding all thyroid therapy. As a matter of fact, it is our opinion that the heart condition grows steadily worse, despite routine measures, when this is done. Patient 16, G. F. (Fig. 3), affords another good example of this. Her mild right- and left-sided cardiac failure was completely relieved by rest in bed and digitalis therapy, but the added cardiac load produced by the administration of as little as 0.1 grain of thyroid was sufficient to cause severe anginal distress. Later, these signs failed to make their appearance with 0.05 grain of desiccated thyroid substance daily. Between the ninety-sixth and one hundred thirtieth days of treatment (Fig. 3), there was gradual improvement in the patient's status, as reflected in increasing activity without cardiac signs, decreasing capillary permeability, and a slowly rising basal metabolic rate. There is reason to believe that the sudden increase in demands upon the heart which followed a sharp increase in the dose of thyroid to 1 grain daily was a precipitating factor in her death from coronary occlusion.

The experiences mentioned serve to emphasize the fact that the doses of thyroid must be small at first and *very gradually* augmented. The actual amount initially selected, the rate of increase, and the stabilization figure will depend upon many factors, but the age of the patient, the known duration of the disease, and the degree of demonstrable impairment of cardiac function are of primary importance. In view of the careful clinical and pathologic studies that have been made of the "myxedema heart,"[9, 13] these points should need no emphasis. Yet, clinically, in our experience they are neglected features of therapy. The death of two patients (Cases 1 and 16) followed comparatively large initial doses of thyroid, or a too sudden, relatively large increase in the amount administered. Other patients showed severe aggravation of symptoms when similarly treated.

As a rule, a daily dose of 0.25 grain of desiccated thyroid substance was tolerated at the beginning of treatment. However, in two cases this amount had to be reduced considerably because of the aggravation

of cardiac symptoms, and in four cases a smaller amount was used initially because of the patient's unsatisfactory cardiac status. In the cases in which treatment was finally adequate, the dosages necessary to keep the patients free of the symptoms of thyroid insufficiency varied from 0.5 to 3 grains daily.

CASE HISTORIES

Case histories for the majority of our patients will be summarized elsewhere.[12] Below appear the detailed records of the three patients whose conditions have been utilized extensively for illustrative purposes in the correlation of data and illumination of discussion. Case numbers here and in Table I are in chronological relation to the series as a whole.

CASE 8.—J. C., a 49-year-old white woman, was admitted to the hospital because of nocturnal "fits," exertional dyspnea, and precordial pain, the first two of several months' duration, and the last mentioned occurring for several days in conjunction with the dyspnea. The fits were described as left-sided "shaking spells," each lasting fifteen to ninety minutes without loss of consciousness, associated with vertigo, blurring of vision, spots before the eyes, and chattering of the teeth. For "more than a year," the patient stated she had been unusually sluggish and had "felt heavy, big, and awkward." For many years she had felt weak, had been pale, and tired easily.

Her father died at the age of 59 years of diabetes. She was one of seven siblings; two sisters "had heart trouble." There was no family history of any thyroid disturbance or of unusual skeletal development. She had had uncomplicated scarlet fever at the age of 11 years, mastoiditis which necessitated operation at the age of 37 years, and pneumonia at the age of 47 years. There had been vague "growing pains" in early life, but the patient had no knowledge of rheumatic fever or its complications. Her menses had begun at the age of 13 years, and had recurred irregularly until the age of 15 years; each period lasted three or four days, with scanty flow. There was complete cessation until the age of 21 years, when, after marriage, the menstrual flow returned at fairly regular intervals until the age of 25 years. Complete amenorrhea followed the birth of her second child at that age.

Physical examination revealed a stockily built, well-nourished, mentally and physically sluggish woman whose height was 59 inches; the lower measurement was 29 inches, and her weight was 134 pounds. Her skin was pale, thickened, coarse, and dry. The supra-orbital, axillary, and pubic hair was scanty, and that of the scalp, coarse and dry. The facies was mongoloid, with thick, heavy lips, slitlike orbital fissures, puffiness of the eyelids, and loss of expression. The tongue was large and thick, and the mouth was open a great deal of the time. The thyroid was readily palpable; the left lobe was somewhat uniformly enlarged, but of normal consistency. The lungs showed evidence of basal congestion. The heart was enlarged, with straightening of the left border. There was a rumbling presystolic and systolic apical murmur, with accentuation of the pulmonic second sound. The ventricular rate was 72; the blood pressure, 112/80. Her knee jerks were sluggish. No pathologic reflexes were elicited. The laboratory data on, or shortly after, admission included a negative urinalysis, negative blood Wassermann and Kahn reactions, and a basal metabolic rate of –39 per cent. The hemoglobin was 89 per cent, the erythrocyte count, 4,080,000 per

cubic millimeter, and the leucocyte count 6,500 per cubic millimeter, with a percentual differential count of polymorphonuclear cells, 60; lymphocytes, 34; transitional forms, 2; and eosinophiles, 4. On two occasions free hydrochloric acid was absent from the stomach contents after the administration of histamine; the total acid was low, never rising above about 10 units. Fasting and hourly blood sugar levels in milligrams per 100 c.c., after the oral administration of 100 Gm. of glucose, were 95, 130, 143, 145, 93, and 95, respectively. The speed of sedimentation of her erythrocytes (Westergren method) was 4 mm. in fifteen minutes, and 39 mm. in an hour. In percentage, her total serum proteins were 7.38; the albumin was 4.74, and the globulin, 2.64, with an albumin-globulin ratio of 1.78. Her icteric index was 6.5; the cephalin flocculation test was negative; the van den Bergh reaction was of the direct negative type; and blood phosphatase was 3 Bodansky units per 100 cubic centimeters. Other blood chemical values in milligrams per 100 c.c. were: calcium, 10; phosphorus, 3.3; total cholesterol, 260; free cholesterol, 76 (34 per cent); chlorides (as sodium chloride), 545; urea nitrogen, 14; and creatinine, 1.2. Roentgenograms of the skull and wrist failed to show any bony abnormalities. Roentgenologic examination of the alimentary tract revealed no evidence of disease. There was enlargement of the cardiac shadow, with straightening of the left border (mitralization). The electrocardiogram showed normal sinus rhythm, with an average rate of 64 per minute. The P-R interval was prolonged to 0.24 second. There was low voltage of all complexes in each of the leads, with an R_2 of 5 mm., no T wave greater than 0.5 mm., and inversion of T_3. The circulation time was 23 seconds (fluorescein method). The capillary permeability was 51 per cent above normal at the ten-minute interval.

Diagnosis.—Myxedema with "myxedema heart"; old, inactive rheumatic heart disease with mitral valvulitis; generalized arteriosclerosis, most marked in the cerebral vessels; and tonic left-sided convulsions resulting from the combined effects of myxedema and cerebral sclerosis.

Her *course* in the hospital is graphically depicted in Fig. 2. Her pulmonary congestion and anginal pain quickly subsided with rest in bed. She was then given desiccated thyroid substance in a dose of ¼ grain daily for nine days, whereupon the angina pectoris returned. After a rest period of nine days, during which cardiac symptoms again disappeared, thyroid medication was resumed with a dose of ⅛ grain daily. This was gradually increased until, at the time of discharge, seventy-four days after admission, she was taking 1 grain daily without untoward reaction. Her circulation time, blood cholesterol, and capillary permeability were normal. Her basal metabolic rate was still low (−19 per cent), and her electrocardiogram was improved, with the appearance of positive T waves and an increase in the height of the QRS complexes. From Fig. 2 it will be noted that a decrease in capillary permeability went hand in hand with an increase in the basal metabolic rate; the former change was greater and more dramatic than the latter. The circulation time returned to normal much more slowly. The patient was finally stabilized on 1½ grain of desiccated thyroid substance daily, with complete disappearance of generalized and cardiac signs of myxedema.

CASE 9.—R. W., a 35-year-old, white married woman, was admitted to the hospital because of excessive nervousness, irritability, apprehensiveness, "inability to accomplish things," coldness, and belching after meals, all of thirteen years' duration and of gradually increasing se-

verity. These symptoms began after an operation for "ruptured appendix, ureteral stone, and dropped right kidney." Hoarseness, dryness of the skin without tendency to perspire even in the summertime, and constipation had been present for several years. Palpitation, substernal oppression, dyspnea, and swelling of the hands and face, in association with a gain of 10 pounds in weight, had been noticed by the patient and her family for four to five months. The patient had been variously treated through twelve years for psychoneurosis, anemia, "kidney disease" and "female trouble."

Most of her earlier history was irrelevant. Her menses began at the age of 12½ years, and had recurred regularly at twenty-eight-day intervals, with a scanty flow lasting three days. Although she had been married for twelve years, she had never experienced normal libido or orgasm, and there had been no children although contraceptives had never been used.

Her father died at the age of 72 years of carcinoma of the stomach. Her mother died at the age of 54 years of "heart trouble." One brother, aged 42 years, had rheumatic heart disease. One sister, now aged 38 years, has been operated on "for a goiter."

Physical examination revealed a pale, cooperative, intelligent, but slowly responding woman, 64½ inches tall and weighing 137 pounds. Her skin and hair were dry, thickened, and coarse. The face was puffy and swollen, particularly about the eyes. Slight exophthalmos was present. Thyroid tissue could be palpated over the thyroid cartilage, but was decreased in amount. The lungs were normal. The heart was not enlarged. The apex beat was not visible or easily palpable. The heart sounds were distant; no thrills or murmurs were present. The ventricular rate was 54, and the blood pressure, 98/78. The extremities were cold, dry, and myxedematous.

Laboratory data on, or shortly after, admission included a negative urinalysis, negative blood Wassermann and Kahn reactions, a negative cephalin flocculation, a negative direct van den Bergh, and a basal metabolic rate of –46 per cent. The icteric index was 6.5 units, and the blood phosphatase, 2.2 Bodansky units. Her blood sugar in milligrams per 100 c.c., fasting, and at half an hour, one and a half, two and a half, and three and a half hours after the ingestion of 100 Gm. of glucose, was 90, 155, 180, 110, and 70, respectively. The total blood proteins were 7.87 per cent; the albumin fraction was 5.35 per cent, the globulin fraction, 2.50 per cent, and the albumin-globulin ratio, 2.12. Other blood chemical values in milligrams per 100 c.c. were: urea nitrogen, 12.1; creatinine, 1.1; phosphorus, 3.5; total cholesterol, 544; free cholesterol, 200 (37 per cent). Her hemoglobin was 69 per cent. There were 3,630,000 erythrocytes and 6,350 leucocytes per cubic millimeter of blood. The percentual partition of leucocytes was: polymorphonuclear forms, 25; lymphocytes, 69; transitional forms, 3; eosinophiles, 2; and basophiles, 1. Her circulation time was 24 seconds (fluorescein method). Her capillary permeability at twenty minutes was 38 per cent above normal. Her electrocardiogram (Fig. 6) showed sinus bradycardia (rate 60), with very low voltage of all complexes. T waves were absent from Lead I and inverted in Leads II and III. Roentgenograms of the skull, chest, wrists, gastrointestinal tract, and biliary passages revealed no organic disease. The heart was slightly enlarged, with a cardiothoracic ratio of 0.51.

Diagnosis.—Myxedema, with myxedema heart.

The *course* of this patient in the hospital is shown graphically in Fig. 4. In addition to the data there charted, her blood proteins were followed serially, and there was a decrease to low normal levels as soon as thyroid therapy became effective. Free and ester fractions of cholesterol are not given in the graph because they were always percentually normal. One-fourth grain of desiccated thyroid substance, begun on the seventh day after admission, produced a rather severe exacerbation of her anginal pain, and not until it was reduced to $\frac{1}{20}$ grain did this disappear. Later the dosage was slowly increased at approximately ten-day intervals, so that, successively, 0.1, 0.25, 0.50. 1, 2, and 3 grains were taken. As judged by the clinical observations, the capillary permeability changes, the blood cholesterol levels, the circulation times, and the electrocardiograms, the patient's myxedema disappeared on or about the fiftieth day after treatment was begun, and after she had received 2 grains of thyroid for five or six days. However, the basal metabolic rate was still extremely low (–29 per cent), and the disease was not deemed to be controlled fully until 3 grains of thyroid had been used for approximately two weeks, at the end of which time the basal metabolic rate was –12 per cent. It was not until this level of dosage was reached that she lost all of her gastrointestinal symptoms and her vague aches and pains. Since her discharge from the hospital, her maintenance dose has remained at 3 grains daily.

CASE 16.—G. F., a 63-year-old, white widow, was admitted to the hospital on the day of an attack later proved to be one of coronary occlusion. She had suffered intermittently from precordial pain for about two years, and had had a severe attack two months prior to admission, which had not, however, confined her to bed. For two years she had noticed sensitiveness to cold, constipation, increasing hoarseness, dryness of the skin and hair, with absence of sweating, and a slow, steady gain in weight. Her past and family histories were noncontributory. Her menses had begun at the age of 13 years, had occurred "monthly," lasting four to five days, and had not been associated with clots, pains, or other distressing symptoms. She had been pregnant three times and had three children. Her menopause appeared spontaneously and apparently asymptomatically at the age of 30 years.

The patient was a moderately obese, rather apathetic person, complaining of precordial pain. Her weight was 146½ pounds; her height, 60½ inches; her temperature, 99° F.; her pulse rate, 100; and her respirations, 28. Her skin was cold, dry, thickened, and tough. The hair was moderately coarse. The heart was enlarged to the left and downward; the heart sounds were faint; and there were no thrills or murmurs. The blood pressure was 140/60, and remained near that level until her death, on the one hundred twenty-seventh day after admission. A few moist râles could be heard at the bases of both lungs. The edge of the liver was palpated two fingerbreadths below the costal margin. There was generalized myxedema, but no evidence of pitting edema in any part of the body.

On, or shortly after, admission, her urinalysis was negative; her blood Wassermann and Kahn reactions, negative; her van den Bergh, direct, negative; her icteric index, 5; her blood phosphatase, 7.7 Bodansky units; her cephalin flocculation, negative; and her basal metabolic rate, –24 per cent. The speed of sedimentation of her erythrocytes was 60 mm. in fifteen minutes and 130 mm. in an hour (Westergren method). The blood albumin, globulin, and total proteins were 4.73, 3.17, and 7.90 per cent, respectively, with an albumin-globulin ratio of 1.48.

Other blood chemical values in milligrams per 100 c.c. were: urea nitrogen, 11; creatinine, 1; phosphorus, 2.3; total cholesterol, 480; and free cholesterol, 120 (25 per cent). The hemoglobin was 82 per cent; there were 3,140,000 erythrocytes and 12,200 leucocytes per cubic millimeter of blood. The electrocardiogram showed rather marked left axis deviation and evidence of posterior wall infarction. Teleroentgenograms of the chest revealed slight enlargement of the heart. Later, after the cardiac condition was well compensated, but before thyroid therapy was begun, the circulation time was 16 seconds, and the capillary permeability at the end of ten minutes, about 151 per cent of normal.

Diagnosis.—Myxedema; coronary sclerosis with coronary occlusion; generalized arteriosclerosis, probably with preexisting hypertension.

Under digitalis, this patient's cardiac failure disappeared rapidly, her pain ceased, and the basal metabolic rate dropped to −42 per cent. On the seventieth day of hospitalization, the administration of thyroid was begun with a dose of $\frac{1}{10}$ grain of the desiccated material daily. On the fourteenth day after it was begun, the patient complained of severe anginal pains; these ceased within two days after the drug was stopped. Seven days later, 0.05 grain daily was administered without ill effect, although the patient was allowed to be up and about the ward. Thirty-three days later, 1 grain of thyroid was administered daily. On the morning of the fifth day thereafter, the patient developed severe precordial pain and went rapidly into shock. An electrocardiogram, taken the next day, showed evidence of a fresh coronary occlusion. The patient died one day later. It is interesting and important that, although 0.05 grain of thyroid improved the extremely low basal metabolic rate and reduced the capillary permeability, it had no constant influence upon the circulation time or marked effect upon the blood cholesterol.

SUMMARY

1. In myxedema, variations in blood proteins are of no value in following the results of therapy.

2. In myxedema with cardiac failure, variations in the weight of the patient, his basal metabolic rate, and his circulation time are of no value in ascertaining his thyroid status at any particular moment.

3. When taken in conjunction with the initial level, i.e., before treatment, the total blood cholesterol has been a very reliable method of ascertaining the degree of thyroid sufficiency in myxedema with cardiac failure, for it is uninfluenced by the latter in the absence of signs of liver damage.

4. An increase in capillary permeability is a constant feature of myxedema. A decrease from the initially high permeability is one of the earliest and most constant signs of improvement.

5. Thyroid therapy must be used cautiously in myxedema with cardiac failure. The dose should be sufficiently small to avoid an aggravation of the cardiac phenomena, but, no matter how severe the failure is, some hormone should be used. An effort should be made to make the initial dose sufficiently large to effect a decrease in capillary permeability.

6. Satisfactory initial daily doses of thyroid hormone, as desiccated thyroid substance, have ranged from 0.05 to 1 grain. In thirteen cases, stabilization was attained through the daily use of amounts varying from 0.5 to 3 grains.

REFERENCES

1. Hanger, F. M.: Flocculation of Cephalin-Cholesterol Emulsions by Pathological Sera, Tr. A. Am. Physicians **53**: 148, 1938.
2. Thudichum, J. L.: A Treatise on the Chemical Constitution of the Brain, London, 1884, Baillière, Tindall & Cox.
3. Pohle, F., and Stewart, J. K.: The Cephalin-Cholesterol Flocculation Test as an Aid in the Diagnosis of Hepatic Disorders, J. Clin. Investigation **20**: 241, 1941.
4. Drekter, I. J.: A New Method for the Direct Determination of Cholesterol, Bull. New York M. Coll. Flower & Fifth Ave. Hosps. **6**: 138, 1943.
5. Lange, K., and Boyd, L. J.: The Technique of the Fluorescein Test to Determine the Adequacy of Circulation in Peripheral Vascular Diseases, the Circulation Time and Capillary Permeability, Bull. New York M. Coll., Flower & Fifth Ave. Hosps. **6**: 78, 1943.
6. Lange, K., and Krewer, S. E.: The Dermofluorometer, J. Lab. & Clin. Med. **28**: 1746, 1943.
7. Klotz, S. D., Schwimmer, D., Drekter, I. J., and McGavack, T. H.: A Fasting-Blood-Sample Procedure in the Differential Diagnosis and Management of Hepatic Disease, Am. J. Digest Dis. **12**: 1, 1945.
8. Lange, K.: Capillary Permeability in Myxedema, Am. J. M. Sc. **207**: 1944.
9. LaDue, J. S.: Myxedema Heart: A Pathological and Therapeutic Study, Ann. Int. Med. **18**: 332, 1943.
10. Schultz, A.: Ueber einen Fall von Athyreosis congenita (Myxödem) mit besonderer Berücksichtigung der dabei beobachteten Muskelveränderungen, Virchows Arch. f. path. Anat. **232**: 302, 1941.
11. Behr, E., and Mulder, J.: Het Myxoedeemhart, een pathologisch-anatomische Bijdrage, Nederl. tijdschr. v. geneesk. **82**: 4303, 1938.
12. Schwimmer, D., Vogel, M., and McGavack, T. H.: In press.
13. Lerman, J., Clark, R. J., and Means, J. H.: The Heart in Myxedema: Electrocardiograms and Roentgen-Ray Measurements Before and After Therapy, Ann. Int. Med. **6**: 1251, 1933.

ELECTROCARDIOGRAPHIC STUDY OF DEFORMITY OF THE CHEST

AMADO R. ADORNO, M.D., ASUNCIÓN, PARAGUAY, AND
PAUL D. WHITE, M.D., BOSTON, MASS.

CARDIAC signs and symptoms produced by chest deformity have been described largely by continental European writers. In 1878, hypertrophy of the right ventricle in a case of high-grade scoliosis was noted by Traube.[1] Since then a large number of articles have appeared in the French,[2-5, 25] Italian,[6] and German literature.[7-9] The best piece of work among them was done in 1899 by Bachmann, who reported 197 autopsy cases of scoliosis, most of which showed right ventricular hypertrophy and dilatation. In later years the role that this factor can play in determining cardiac failure has become more prominent in the English literature.[10-22]

In spite of all these investigations we have only very scattered data from the electrocardiographic standpoint. The majority of investigators agree that a high percentage of patients with chest deformity show hypertrophy and dilatation of the right-sided cavities in so far as the pathologic examination is concerned, but relatively few electrocardiograms have been mentioned. These have shown right axis deviation or a tendency toward it.[18, 20] Edeiken[13] took electrocardiograms of eighteen otherwise unselected patients with deformed chests and reported that "except for axis deviation the tracings were normal in 16 instances."

PRESENT STUDY

In order to obtain more adequate information than now exists concerning the effect of chest deformity, as such, on the electrocardiogram, we have studied one hundred deformed patients. We have purposely avoided patients with obvious cardiac damage, myocardial, valvular, or pericardial. Moreover, we have selected patients without pulmonary disease which might add an extra strain on the right side of the heart, in addition to that due to the deformity of the chest itself. Under these conditions we believe that the electrocardiographic abnormalities which we have found have not been influenced by heart or lung disease per se.

We selected cases of young persons, mostly between 15 and 25 years of age, with normal blood pressure and without râles at the bases of the lungs, constant heart murmurs, gallop rhythm, engorged jugular veins, increased liver volume, or pitting edema. We found that some symptoms, such as slight or mild dyspnea on effort, are not reliable clues of myocardial reserve because of the great diminution of the vital capacity in most of our cases.

Also, we carried out roentgenologic studies of the heart and lungs, looking for any definite partial or total enlargement of the heart and

Received for publication June 23, 1944.

also for pulmonary fibrosis or emphysema that might be detected by this procedure. The limitations of roentgenologic examination of the heart in chest deformities must, however, be kept in mind.

After exclusion of heart and lung disease by the patient's history, physical examination, and roentgenologic observations, the vital capacity was measured and the electrocardiogram was taken. The standard limb leads and chest leads CF_2, CF_4, and CF_5 in the sitting and recumbent positions were recorded on each patient.

RESULTS

The observations that we made from the routine examination of these selected patients are as follows:

There were seventeen patients with an electrical axis of between 80 and 95 degrees toward the right, two patients with left axis deviation, and eighty-one patients, the great majority, with a normal electrical axis (Table I).

When the axis was studied in persons with a marked decrease in the vital capacity, the percentages changed slightly. Thirty-two patients with less than 50 per cent of normal vital capacity were observed from this point of view, and the distribution was as follows: 25 per cent toward the right, 3.4 per cent toward the left, and 71.6 per cent normal. We did not find a close relationship between the vital capacity and the electrical axis. In the group with less than 50 per cent of normal vital capacity, with the proportion of right axis deviation slightly increased, we found one case with 38 per cent of normal vital capacity and an axis of 32 degrees, and in another, with 30 per cent of normal vital capacity, the axis was –12 degrees.

Then we tried to correlate the electrical axis with the curve of the spine. There were sixty-seven patients with right dorsal, left lumbar scoliosis (Group 1), nineteen with left dorsal, right lumbar scoliosis (Group 2), five with the convexity entirely to the left (Group 3), one with the convexity entirely to the right (Group 4), six patients with predominant kyphosis (Group 5), and two with funnel chest (Group 6).

In our first group, 26.8 per cent of the patients had deviation toward the right and 73.2 per cent were normal. There were none with deviation toward the left. In the second group, 15.6 per cent were toward the left and 84.4 per cent were normal. There were none toward the right. In the third group we found 100 per cent with normal axes. In the fourth, the only patient in the group had a normal axis. In the fifth group (kyphosis) there were 100 per cent with normal axes, and in the last group both patients had normal axes.

Because we observed that in thirty-one instances the axis shifted toward the right instead of to the left when the patients changed from the sitting position to recumbency, we tried to correlate these observations with the type of the deformity, but we did not find any relationship with either the build or the vital capacity of the patients.

TABLE I

NUMBER	AGE (YR.)	TYPE OF DEFORMITY	VITAL CAPACITY (PER CENT OF NORMAL)	AXIS SITTING DEGREES	AXIS RECUMBENT DEGREES
1. R. V.	14	Right dorsal, left lumbar	42	45	52
2. M. M.	24	Right dorsal, left lumbar	20	90	80
3. H. A.	13	Right dorsal, left lumbar	16	110	105
4. P. V.	12	Total left	41	52	30
5. E. W.	22	Right dorsal, left lumbar	39	56	48
6. D. R.	25	Right dorsal, left lumbar	112	33	33
7. G. T.	15	Right dorsal, left lumbar	38	32	30
8. J. McC.	14	Right dorsal, left lumbar	81	92	80
9. C. B. C.	13	Right dorsal, left lumbar	68	87	80
10. R. B.	24	Right dorsal, left lumbar	42	20	23
11. W. D.	19	Kyphosis	68	43	55
12. L. F.	15	Left total	52	85	85
13. B. E.	15	Right dorsal, left lumbar	35	90	90
14. E. S.	13	Right dorsal, left lumbar	92	85	70
15. A. M.	26	Right dorsal, left lumbar	32	20	25
16. M. F.	19	Right dorsal, left lumbar	66	90	85
17. J. S.	14	Left dorsal, right lumbar	68	68	60
18. G. G.	13	Right dorsal, left lumbar	78	30	30
19. A. R.	20	Right dorsal, left lumbar	46	70	65
20. M. D.	22	Right dorsal, left lumbar	35	92	86
21. R. F.	23	Left dorsal, right lumbar	61	12	12
22. P. M.	20	Left dorsal, right lumbar	71	60	60
23. J. T.	19	Kyphosis	42	50	50
24. J. H.	25	Right dorsal, left lumbar	36	95	100
25. M. N.	14	Right dorsal, left lumbar	52	120	120
26. L. P.	18	Right dorsal, left lumbar	64	30	30
27. L. K.	19	Right dorsal, left lumbar	47	116	110
28. R. McN.	14	Funnel chest	47	70	72
29. E. S.	15	Left dorsal, right lumbar	85	60	58
30. M. C.	25	Right total	97	62	60
31. B. G.	14	Kyphosis	82	68	56
32. N. G.	17	Left dorsal, right lumbar	90	48	36
33. A. R.	23	Right dorsal, left lumbar	53	92	90
34. A. P.	14	Left dorsal, right lumbar	28	44	66
35. J. C.	22	Left dorsal, right lumbar	37	55	55
36. H. E.	20	Left dorsal, right lumbar	100	70	66
37. I. A.	22	Right dorsal, left lumbar	65	90	90
38. A. B.	19	Left dorsal, right lumbar	45	40	50
39. D. P.	15	Left dorsal, right lumbar	68	15	30
40. E. R.	20	Right dorsal, left lumbar	66	78	70
41. M. McN.	12	Left dorsal, right lumbar	47	52	50
42. P. DeN.	15	Right dorsal, left lumbar	40	60	90
43. M. McK.	41	Right dorsal, left lumbar	52	50	60
44. R. DeP.	8	Funnel chest	42	30	30
45. N. C.	17	Right dorsal, left lumbar	91	58	38
46. L. G.	13	Right dorsal, left lumbar	61	120	115
47. J. M.	18	Right dorsal, left lumbar	40	50	60
48. C. S.	17	Left dorsal, right lumbar	69	56	62
49. A. B.	22	Left total	97	56	60
50. A. S.	14	Left dorsal, right lumbar	90	55	70
51. E. W.	20	Right dorsal, left lumbar	61	65	57
52. B. P.	10	Right dorsal, left lumbar	72	55	55
53. B. M.	30	Left dorsal, right lumbar	115	18	30
54. M. S.	17	Right dorsal, left lumbar	66	68	63
55. N. W.	57	Left dorsal, right lumbar	30	-12	-12
56. M. K.	24	Right dorsal, left lumbar	57	70	70
57. A. K.	15	Right dorsal, left lumbar	75	110	105
58. J. N.	14	Right dorsal, left lumbar	82	90	90
59. E. K.	19	Left total	49	62	40

TABLE I—CONT'D

NUMBER	AGE (YR.)	TYPE OF DEFORMITY	VITAL CAPACITY (PER CENT OF NORMAL)	AXIS SITTING DEGREES	AXIS RECUMBENT DEGREES
60. A. C.	19	Right dorsal, left lumbar	65	90	90
61. E. G.	14	Right dorsal, left lumbar	59	56	42
62. E. S.	14	Right dorsal, left lumbar	80	81	78
63. A. D.	15	Right dorsal, left lumbar	81	75	82
64. R. W.	15	Kyphosis	26	76	76
65. R. M.	18	Right dorsal, left lumbar	29	43	41
66. H.H.	21	Right dorsal, left lumbar	75	55	53
67. M. D.	39	Right dorsal, left lumbar	30	30	20
68. R. C.	16	Right dorsal, left lumbar	72	72	55
69. I. S.	13	Left dorsal, right lumbar	93	30	40
70. A. B.	17	Right dorsal, left lumbar	88	87	90
71. G. M.	26	Right dorsal, left lumbar	89	18	48
72. H. B.	13	Right dorsal, left lumbar	47	70	55
73. L. B.	13	Right dorsal, left lumbar	45	55	55
74. Y. T.	17	Right dorsal, left lumbar	73	70	74
75. G. F.	22	Kyphosis	62	85	70
76. L. L.	22	Right dorsal, left lumbar	56	40	62
77. E. P.	22	Right dorsal, left lumbar	49	50	60
78. A. C.	35	Right dorsal, left lumbar	71	48	53
79. J. F.	20	Right dorsal, left lumbar	43	82	80
80. M. O'C.	15	Left total	84	30	30
81. H. R.	23	Right dorsal, left lumbar	94	6	6
82. F. D.	14	Kyphosis	110	76	82
83. C. S.	12	Right dorsal, left lumbar	54	30	30
84. P. N.	14	Right dorsal, left lumbar	93	78	70
85. A. H.	17	Right dorsal, left lumbar	80	19	79
86. M. F.	17	Right dorsal, left lumbar	84	52	58
87. E. St. I.	14	Right dorsal, left lumbar	83	66	73
88. M. O'C.	39	Right dorsal, left lumbar	73	38	45
89. P. K.	16	Left dorsal, right lumbar	107	−3	−18
90. B. H.	15	Right dorsal, left lumbar	62	113	108
91. L. P.	20	Right dorsal, left lumbar	30	30	36
92. B. F.	17	Left dorsal, right lumbar	59	68	56
93. A. D'E.	22	Right dorsal, left lumbar	86	27	30
94. E. K.	16	Right dorsal, left lumbar	93	90	80
95. J. O.	18	Left dorsal, right lumbar	93	38	49
96. V. O.	13	Right dorsal, left lumbar	57	50	42
97. R. L.	17	Right dorsal, left lumbar	95	75	70
98. H. P.	23	Right dorsal, left lumbar	94	35	40
99. M. T.	16	Right dorsal, left lumbar	83	41	45
100. C. M.	11	Right dorsal, left lumbar	59	66	72

In considering the P wave, we observed that this deflection was either peaked or notched, or both at the same time, in thirty-two instances in Lead II, in five in Lead I, and in nineteen in Lead III. The height was no more than 2 or 3 mm., but the shape was very similar to that of the P waves in mitral stenosis or congenital heart disease.

With regard to the QRS deflection, we noticed that, in spite of the duration, which was not more than 0.10 second, it was frequently slurred or notched; the height was more than 5 mm. in the limb leads and 10 mm. in the chest leads.

In the S-T segments no significant changes were found.

So far as the T waves are concerned, nothing abnormal was found in the limb leads. In the chest leads the T waves were inverted in

twenty-three cases (six males and seventeen females). Among these patients, nine were less than 15 years old and fourteen were 15 years or more. The mean age was 16.3 years. The observations were as follows: T in CF_2 inverted seven times in the sitting position and seventeen times in recumbency; T in CF_4 inverted three times in the sitting position and three times in recumbency; T in CF_5 inverted twice in the sitting position and once in recumbency.

The following are the histories and electrocardiograms of two interesting patients.

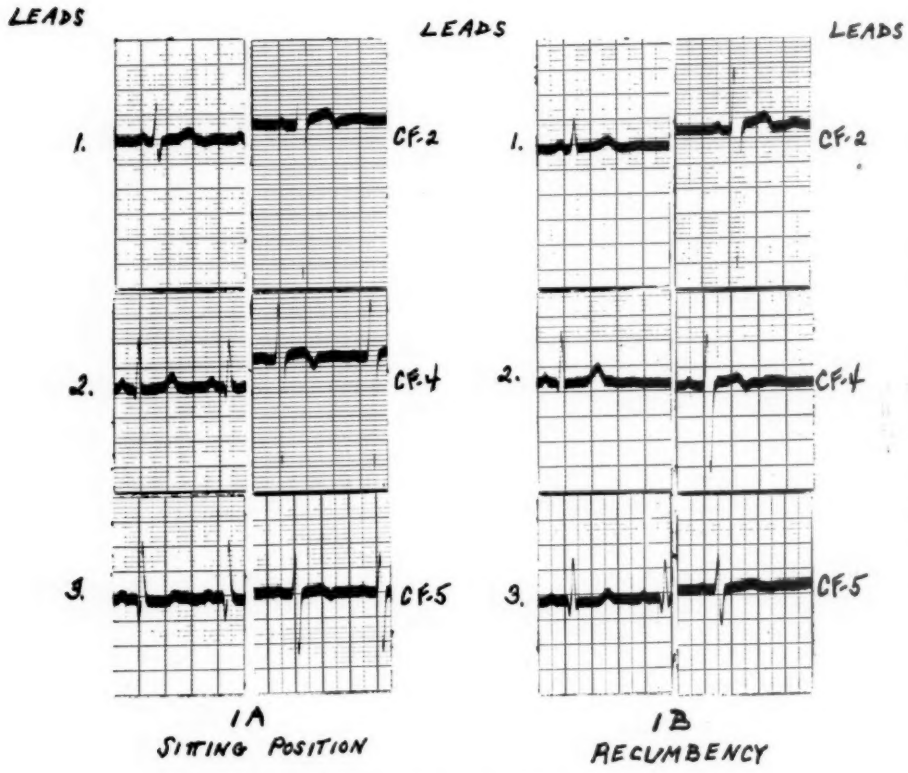


Fig. 1.—Electrocardiograms of Case 1, E. S.

CASE 1.—The first, E. S., was a 15-year-old schoolgirl who came to the hospital with the chief complaint of deformity of the chest. This abnormality was first noted when she was 5 years old. Her mother therefore took her to the Children's Hospital in Boston, where roentgenologic studies revealed one hemidorsal vertebra causing scoliosis. The patient was treated for a number of years with exercises, and has recently been placed in a plaster cast.

Past History.—Measles and chicken pox. No other disease. No history of rheumatic fever. No operations. Very active and athletic. No cardiac, respiratory, or gastrointestinal complaints.

Family History.—No family history of any similar or other deformity.

Physical Examination.—Well-developed girl with a conspicuous left dorsal scoliosis. The right lumbar scoliosis was not very marked. Her reflexes were normal. The heart was not enlarged and there were no murmurs. Blood pressure, 110/70. Lungs normal.

An electrocardiogram in the sitting position (Fig. 1, *A*) revealed slight sinus arrhythmia, an average rate of 80, a P-R interval of 0.14 second, normal axis, prominence of S_1 and Q_3, slight late sagging of $S\text{-}T_3$, and upright T waves in Leads I, II, and III. In the chest leads there were diphasic T waves in CF_2 and late inversion of the T waves in CF_4 and CF_5. In recumbency the electrocardiogram (Fig. 1, *B*) showed marked sinus arrhythmia and an average rate of 75. S_1 had disappeared and Q_3 was not nearly so prominent. The T waves in Leads II and III had become more upright and pointed. In the chest leads, T in CF_2 had become more upright, T in CF_4 less inverted, and T in CF_5 upright.

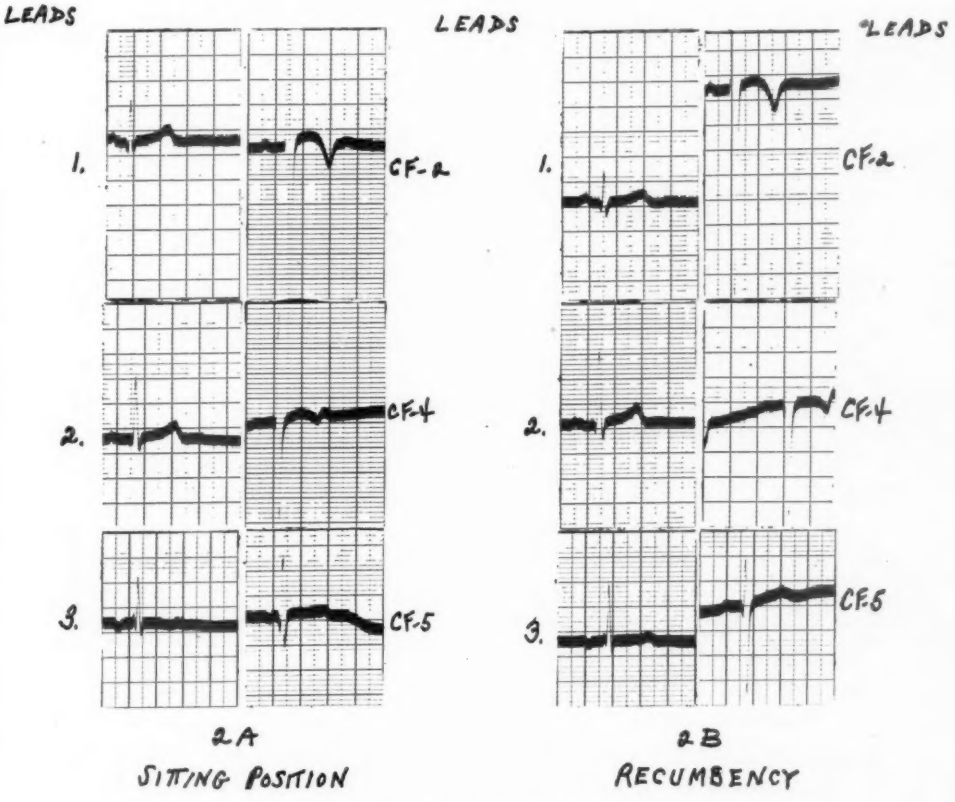


Fig. 2.—Electrocardiograms of Case 2, J. T.

CASE 2.—In January, 1942, a 19-year-old, single man, J. T., was admitted to the hospital because of curvature of the spine. This curvature was first noted at the age of 10 years, and had become progressively worse. He entered because of attacks of pain in the lower right chest region for three years, pain which was sharp and shooting in nature.

Past History.—Only chicken pox. No history of rheumatic fever. Rare sore throat. For several years he had had slight dyspnea on exertion, without cough or hemoptysis.

Family History.—Irrelevant.

Physical Examination.—Patient had a marked left dorsal scoliosis, with marked high thoracic kyphosis. *Heart:* apex impulse felt in fifth intercostal space, 1 cm. inside the midclavicular line. Sounds regular, of good quality. No murmurs. The pulmonary second sound was louder than the aortic second. Blood pressure, 123/75. Lungs negative. Liver not tender and apparently not enlarged. Roentgenologic examination showed nothing particularly wrong with the heart.

At this time a spinal fusion was performed, and since then has become stabilized.

An electrocardiogram in the sitting position (Fig. 2, *A*) revealed normal rhythm, a rate of 58, a P-R interval of 0.18 second, slight elevation of S-$T_{1, 2}$, upright and pointed $T_{1, 2}$, and a rather isoelectric T_3. In the chest leads there were an inverted T in CF_2, a diphasic T in CF_4, and an upright T in CF_5. In recumbency, T_1 became lower and T_3 higher, the T in CF_2 and CF_4 more deeply inverted, and the T in CF_5 upright (Fig. 2, *B*).

DISCUSSION

The deviation of the axis according to the type of the spinal curvature can be explained by the roentgenograms which we observed in our patients. We have seen that, with right convex scoliosis, the heart is shifted to the left and the left border appears straightened, which Roesler calls "mitral configuration." With the less frequent left convex scoliosis, the heart is shifted to the right and the aortic shadow appears widened. The same picture, but less marked, was presented by the patients with right total, and left total, curvature, respectively. In kyphosis we did not find any striking difference from the normal, although sometimes the heart lay in a horizontal position. We made out no abnormality in the roentgenograms in our cases of funnel chest. Nevertheless, in two cases especially, which we do not discuss here because of associated congenital heart disease and probable arachnodactyly, there was a very marked shift of the heart toward the left.

The great preponderance of cases of normal axis in scoliosis can be explained by (1) displacement of the whole heart without rotation on its anteroposterior or longitudinal axis, such as is likely to occur in funnel chest, or (2) rotation around the longitudinal axis, which could compensate for the rotation around the anteroposterior axis. The effect of rotation of the heart about the longitudinal axis has been studied by two groups of investigators. Boden and Neukirch[23] found that rotation of the isolated perfused heart about the long axis to the left resulted in a tendency to right preponderance, whereas rotation to the right gave opposite effects. On the other hand, Meek and Wilson[24] found that displacement of the heart to the right or the left usually caused a combined rotation on both axes, and produced electrocardi-

ographic changes which cannot be predicted because of the opposing effects of simultaneous rotation around the longitudinal and anteroposterior axes.

So far as the literature about cases of pulmonocardiac failure as a result of spinal deformities is concerned, the frequency of right axis deviation is much higher than in our series, which is presented without regard to the type of curvature. It is logical to believe that the atelectasis, sclerosis, and superimposed infections which frequently supervene in these cases of long standing throw an increasing strain on the right side of the heart, producing a tendency of the axis to lean toward the right. Thus, the real axis produced by the deformity itself is overlapped by the additional factors which finally give the picture of chronic cor pulmonale. The high proportion of inverted T waves in Lead CF_2 in our cases can be explained by the fact that we have more cases with right dorsal, left lumbar scoliosis; this increases the possibility that we actually have the CF_1 pattern, instead of CF_2, in spite of the standard location of electrodes.

SUMMARY AND CONCLUSIONS

We have carried out electrocardiographic studies in one hundred cases of chest deformity without evident cardiac or pulmonary disease.

The results were as follows:

1. In right dorsal, left lumbar scoliosis, right axis deviation was present in 26.8 per cent of the cases, and a normal axis in 73.2 per cent.

2. In left dorsal, right lumbar scoliosis, left axis deviation was present in 15.6 per cent of the cases, and a normal axis in 84.4 per cent.

3. In total left or right scoliosis, in kyphosis, and in funnel chest, all the patients presented a normal axis.

The great percentage (80 per cent) of normal axes in the whole group is explained either by a total displacement of the whole heart, without rotation, or by combined rotation on both longitudinal and anteroposterior axes, with neutralization because of their opposing effects.

The T waves were normal in limb leads but inverted in a minority of the cases in the precordial leads, varying somewhat with the position of the patient; this is to be ascribed, in part at least, to the unusual relationship of heart position to the external landmarks of the thorax.

The authors would like to express their appreciation to Miss Deborah Hanson and Miss Louise Wheeler of the Cardiac Laboratory of the Massachusetts General Hospital for their help in the preparation of this paper.

REFERENCES

1. Traube, L.: Quoted by Boas.[15]
2. Barié, E.: Le coeur dans les deviations du rachis et dans les déformations thoraciques, La Semaine Médicale **24**: 65, 1904.
3. Dedic, S.: La cardiopathie cyphotique, Arch. d. mal. du cœur **23**: 33, 1930.
4. J. Belval, Ducrocq, R., Francois, P., et Honorez, P.: Déformations médiastinales observées dans deux cas de cyphose, Ann. d'anat. path. **16**: 1067, 1940.

5. Caussade, G., et Tardieu, A.: Sur les troubles cardio-pulmonaires des gibbeux et leurs rapports avec l'etiologie tuberculeuse, J. méd. franc. **21:** 195, 1932.
6. Pisani, A.: Sopra le alterazioni cardio-polmonari che si riscontrano nella cifoscolliosi, Gazz. d. osp. **25:** 1436, 1904.
7. Klawanksy, G.: Hochgradige mechanische Aortenstenose durch Kyphoskoliose, Klin. Wchnschr. **4:** 831, 1925.
8. Bachmann, M.: Die Veränderungen an den inneren Organen bei hochgradigen Skoliosen und Kyphoskoliosen. Bibliotheca Med., Stuttgart, 1899, Abthiel D. Heft 4.
9. Rieder, J.: Quoted by Boas.[15]
10. Carr, J. G.: The Cardiac Complications of Trichterbrust, Ann. Int. Med. **6:** 885, 1933.
11. Finley, F. G.: Spinal Deformity as a Cause of Cardiac Hypertrophy and Dilatation, Canad. M. A. J. **11:** 719, 1921.
12. Coombs, C. F.: Fatal Cardiac Failure Occurring in Persons With Angular Deformity of the Spine, Brit. J. Surg. **18:** 326, 1930.
13. Edeiken, J.: The Effect of Spinal Deformity on the Heart, Am. J. M. Sc. **186:** 99, 1933.
14. Case Records of the Massachusetts General Hospital. Case 19432. The Interesting Result of Severe Deformity of the Thorax, New England J. Med. **209:** 854, 1933.
15. Boas, E. P.: The Cardiovascular Complications of Kyphoscoliosis, With Report of a Case of Paroxysmal Auricular Fibrillation, Am. J. M. Sc. **166:** 89, 1923.
16. Edeiken, J., and Wolferth, C. C.: The Heart in Funnel Chest, Am. J. M. Sc. **184:** 445, 1932.
17. Roesler, H.: Clinical Roentgenology of the Cardiovascular System, Springfield, 1937, Charles C Thomas, pp. 21, 149, and 181.
18. Kerwin, A. J.: Pulmonocardiac Failure as Result of Spinal Deformity, Report of 5 Cases, Arch. Int. Med. **69:** 560, 1942.
19. Farmer, H. E.: Pulmonocardiac Failure, J. Nat. M. A. **34:** 53, 1942.
20. Chapman, E. M., Dill, D. B., and Graybiel, A.: The Decrease in Functional Capacity of the Lungs and Heart Resulting From Deformities of the Chest: Pulmonocardiac Failure, Medicine **18:** 167, 1939.
21. Nathanson, M. H.: Electrocardiographic Study of Movements of the Heart With Changes of Posture, Proc. Soc. Exper. Biol. & Med. **28:** 766, 1931.
22. Master, A. M.: The Electrocardiogram and X-Ray Configuration of the Heart, Philadelphia, 1939, Lea and Febiger, pp. 208, 210.
23. Boden and Neukirch: Quoted by Nathanson.[21]
24. Meek, W. J., and Wilson, A.: The Effect of Changes in Position of the Heart on the QRS Complex of the Electrocardiogram, Arch. Int. Med. **36:** 614, 1925.
25. Dumas, A.: L'hypertension des bossus et des scoliotiques, Lyon méd. **151:** 134, 1933.

AURICULAR PREMATURE SYSTOLE

I. Aberration of the Ventricular Complex in the Electrocardiogram

Kurt Berliner, M.D., and Leon P. Lewithin, M.D.
New York, N. Y.

AURICULAR premature systoles are characterized, in the electrocardiogram, by premature auricular (P) waves of abnormal contour. Their ventricular deflections (QRS-T complexes) may be identical with those of the normal beats or may differ from them. If they differ, we speak of "aberration." The term was introduced by Lewis,[1] and the abnormality of the ventricular complexes was attributed by him "to deficient conduction along certain tracts of the junctional tissues."[2] The literature contains no satisfactory explanation of aberration, and, in general, little importance has so far been attached to it. It seemed to us that so tangible an electrocardiographic finding might have greater significance. It might, for instance, be found to reflect definite pathologic changes in the heart; in that event, it would yield information not heretofore obtainable from the electrocardiogram. With that possibility in mind, we decided to study the phenomenon of aberration. Our investigation aims at establishing its relative frequency and some of the factors which determine its occurrence. It includes a correlation of clinical and electrocardiographic observations. This correlation attempts to demonstrate the clinical significance of aberration.

MATERIAL AND METHOD

The electrocardiograms of 201 patients were collected. Each electrocardiogram consisted of the three standard leads and one chest lead, IVF, except for 76 older electrocardiograms in which no chest lead was taken. In two cases, on the other hand, two chest leads, CF_2 and CF_4, were taken. The length of each lead strip was 25 centimeters. Many patients exhibited APS* in more than one record, but only one record was used for analysis (except in the clinical part of our study). Each electrocardiogram was first interpreted; next, a count of the number of APS per lead was taken; then, each APS was analyzed as to the degree of prematurity (its location in relation to the preceding normal beat). The following terminology was introduced for purposes of classification:

Location I (late APS): The P wave of the APS does not touch the T wave of the preceding beat (Fig. 2, *A* and *B*; Fig. 11, *B*, x_2).

From the Department of Cardiology, Sydenham Hospital, New York, N. Y.
Received for publication June 24, 1944.

*APS will be used as an abbreviation for auricular premature systole throughout this paper.

TABLE I

DIFFERENT GRADES OF ABERRATION IN 525 TYPES OF AURICULAR PREMATURE SYSTOLES (APS)

NO ABERRATION AT ALL	NO ABERRATION OF QRS, BUT ABERRATION OF RS-T SEGMENT OR T WAVE	FIRST DEGREE ABERRATION							SECOND DEGREE ABERRATION (TWO FEATURES OF QRS CHANGED)	THIRD DEGREE ABERRATION (THREE FEATURES OF QRS CHANGED)	FOURTH DEGREE ABERRATION (FOUR FEATURES OF QRS CHANGED)	BLOCKED APS	TOTAL
		QRS CHANGED IN AMPLITUDE ONLY	QRS CHANGED IN DIRECTION ONLY	QRS CHANGED IN DURATION ONLY	QRS CHANGED IN CONFIGURATION ONLY	R TALLER, S SMALLER OR VICE VERSA	R THE SAME, S DEEPER OR S THE SAME, R TALLER	DIFFERENCE IN SIZE OF Q ONLY					
137	42	79	0	10	42	33	2	13	86	45	28	8	525

Location II (fairly late APS): The P wave of the APS barely touches the descending limb of the T wave of the preceding beat (Fig. 1; Fig. 11, *B*, x_1).

Location III (moderately early APS): The P wave of the APS is superimposed on the descending limb of the preceding T wave (Fig. 2, *C*; Fig. 8, *C*).

Location IV (early APS): The P wave of the APS is superimposed on the ascending limb of the preceding T wave (Fig. 9, *B*; Fig. 11, *A*, x_2).

Location V (very early APS): The P wave of the APS is superimposed on the preceding RS-T segment close to the QRS complex (Fig. 8, *A*).

Twenty-nine records exhibited only one APS per record. One hundred seventy-two, however, showed two or more APS per record. Of the latter, twenty-two showed that all of the APS were of the same location. These APS were classified by us as being of one and the same type. One hundred fifty records showed multiple APS of varying location, and these were classified by us as APS of different types. To give an example: If one record contained three APS, one of location I, another of location III, and a third of location V, the APS were classified as of three different types. The total number of APS counted by us was 1,306; the number of different types found was 525.

Our patients varied in age from 2 to 83 years. Thirty-six patients died during the period of observation; post-mortem examinations were performed on thirteen of these. The clinical charts of all patients were analyzed for diagnosis, and evidence of cardiovascular disease, if found, was carefully noted.

Frequency of Aberration.—The literature contains conflicting statements concerning the frequency of aberration. White,[3] White and Stevens,[4] and Carter[5] estimate that "about half the cases that show auricular premature beats show also varying abnormality of spread of excitation wave through the ventricle." Pardee,[6] on the other hand, states that the ventricular complexes of auricular premature systoles are "*always* slightly different from the other ventricular complexes of the record," and he points out that "this difference is evident in records showing the auricular premature beats in three leads; the curve may be but little changed in any one lead, and yet quite a variant in the other two." Our own observations show definitely that aberrant ventricular complexes are much more frequent than normal ones. Of our 525 different types of APS, eight were blocked, i.e., they had no ventricular complexes at all. Of the remaining 517 types, 137, only a little more than one-fourth, showed no aberration at all (Table I). The figure 137 would have been still smaller, and the percentage of APS showing aberration still greater, if all of our records had included one or more chest leads. This would have been so for two reasons: first, with a larger number of leads the probability that aberration would appear would have been greater;[6] second, chest leads, as such, often magnify aberration, and thereby aid in recognizing it (Fig. 1). In any event, our analysis shows that APS with aberration are much more

frequent than APS without aberration. Besides being rarer, APS without aberration are also more easily overlooked (Fig. 2). They may be particularly inconspicuous if all the P waves of the respective lead are of low amplitude. Furthermore, they may occur late in diastole and may then be so spaced that the distance from the preceding normal beat looks almost normal (Fig. 2, *A*). In other cases, the disturbance of

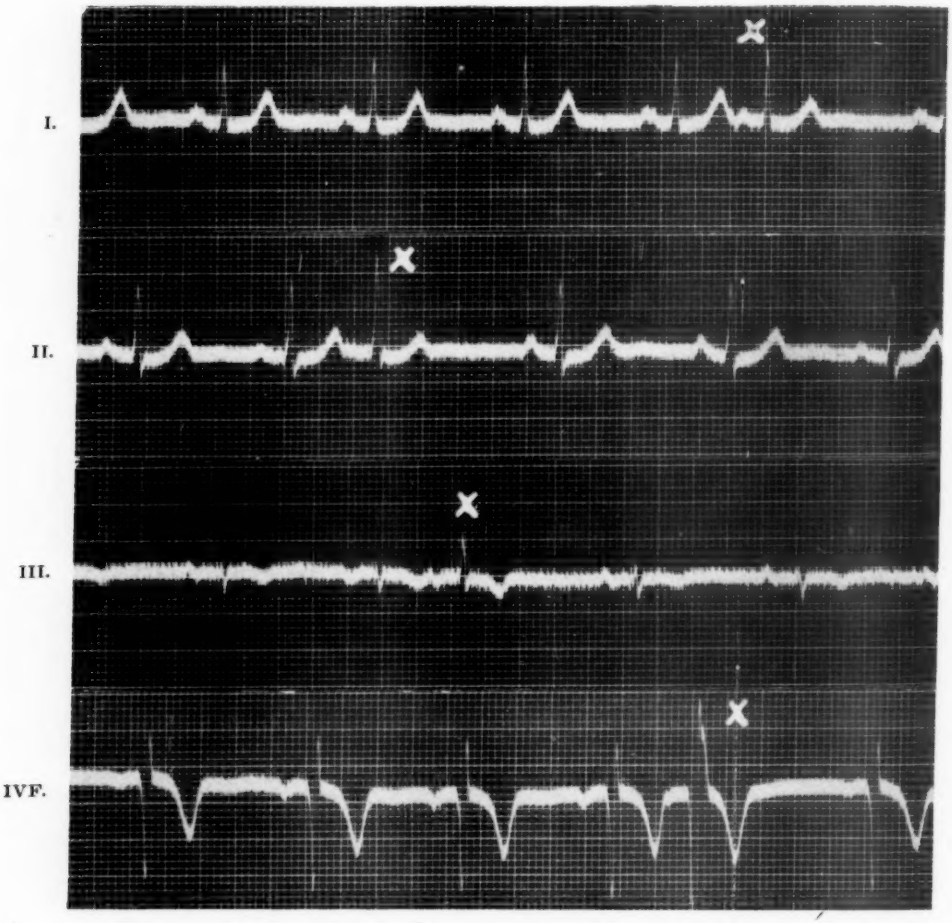


Fig. 1.—A four-lead electrocardiogram. Aberration of the APS is most marked in the chest lead.

rhythm may be easily recognized, but may be misinterpreted as sinus arrhythmia (Fig. 3).*

Aberration of RS-T or of T Only (Fig. 4).—The QRS complexes of APS may be identical with those of the normal beats, but the RS-T seg-

*Sinus arrhythmia is the result of an increase in vagal tone; the development of APS also appears to be favored by an increase in vagal tone. Sinus arrhythmia and APS may, therefore, coexist. If such APS lack aberration, the differentiation between the two conditions may be difficult. In that case it may be advisable to take several chest leads; in one of the chest leads, the ventricular complexes, or the T waves only, may show aberration, and thus establish the diagnosis of APS.

ments or the T waves, or both, may be aberrant. In our series, 43 of the 517 types showed this form of limited aberration. Not infrequently, the aberration of the T waves presented itself in the chest lead only, which is probably due to the fact that in chest leads all T waves are usually larger, and deflections of the RS-T segment are normally more pronounced than in the limb leads (Fig. 5). The more widespread use of multiple chest leads will undoubtedly increase the number of APS discovered electrocardiographically.

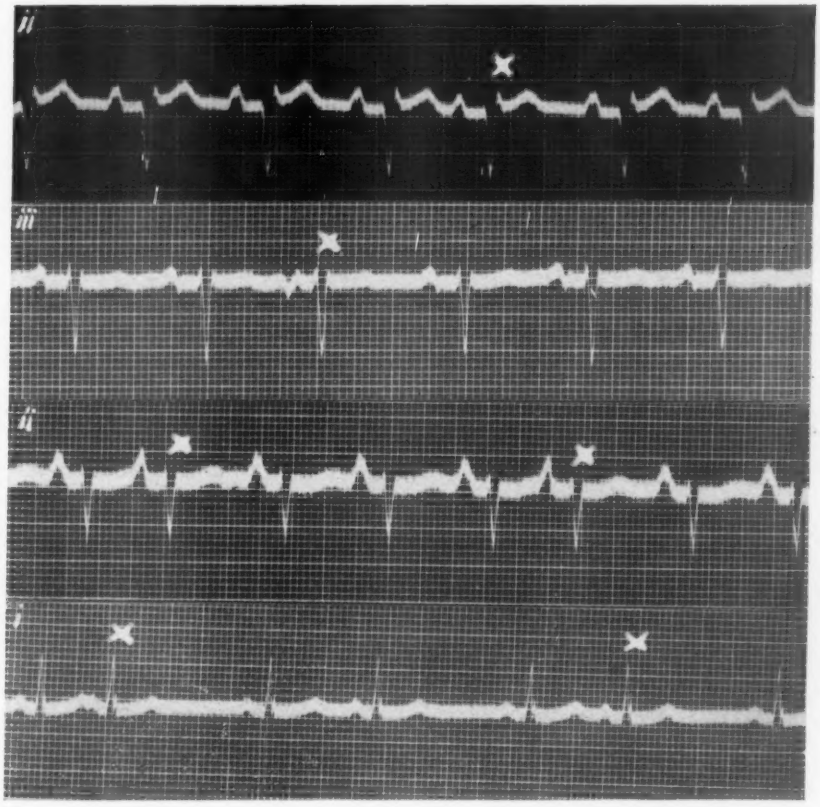


Fig. 2.—APS without any aberration (four cases).

The T-wave aberration in limb leads or chest leads consisted of an increase or decrease in the size of the T wave, a change in its shape, rarely a change in its direction, or a combination of these changes, with or without elevation or depression of the RS-T segment.

Aberration of QRS.—In the majority of APS, 337 of the 517 types, aberration of the QRS complexes was present. This varied in degree from slight changes in amplitude to marked changes in height, duration, configuration, and direction, resulting in truly bizarre complexes. Aberration of QRS was, as a rule, associated with aberration of T, and there was usually parallelism in the degree of both changes.

The most frequent single change was increase or decrease in the amplitude of QRS (Fig. 6, *A*). It occurred, unaccompanied by other changes, in 79 of the 517 types of APS. The increase or decrease in height was usually slight, yet greater than the amplitude variations of normal beats; it often greatly aided in the recognition of the APS. In the chest leads, amplitude variations of APS were usually greater than in the limb leads. Very marked amplitude changes rarely occurred alone, but were usually associated with changes in the duration, configuration, or direction of the QRS complexes. Frequently the total amplitude was the same as that of the normal beats, but the R waves were lower and the S waves deeper, or the R waves taller and the S waves less deep; this occurred as the only aberration in 35 of 517 types.

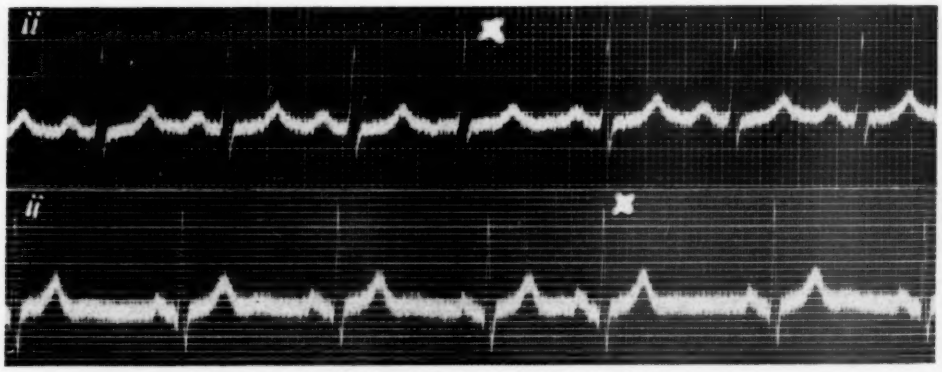


Fig. 3.—APS simulating sinus arrhythmia (two cases).

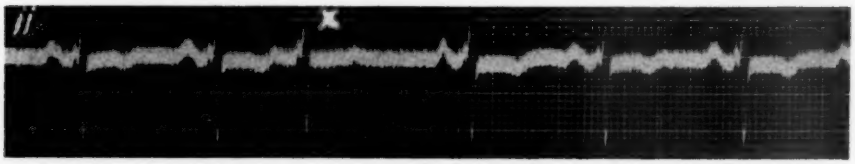


Fig. 4.—An APS with aberration limited to the RS-T segment and T wave.

Changes in the direction of QRS were never found alone, but always in conjunction with changes in amplitude, duration, or configuration, which produced the more marked degrees of aberration (Fig. 6, *B*).

Changes in the duration of the QRS complex were seldom found alone, viz., in only ten of 517 types, and were then usually minor (Fig. 6, *C*). The major changes in duration again were found only in conjunction with changes of amplitude, configuration, or direction.

Changes in configuration were more common (Fig. 6, *D*). Slurring or notching in the QRS complex of the APS as the only sign of aberration occurred in 42 of the 517 types. The more marked degrees of slurring or notching were usually associated with other changes, especially with changes in amplitude, or with changes in amplitude, duration, and

direction. Another change in configuration occasionally found was the appearance (or disappearance) of a Q wave. This occurred as the only demonstrable aberration in 13 of 517 types.

Higher Degrees of Aberration.—The higher degrees of aberration were less frequent than the lower (Table I). For purposes of comparison we grouped all types of APS with only *one* kind of change,

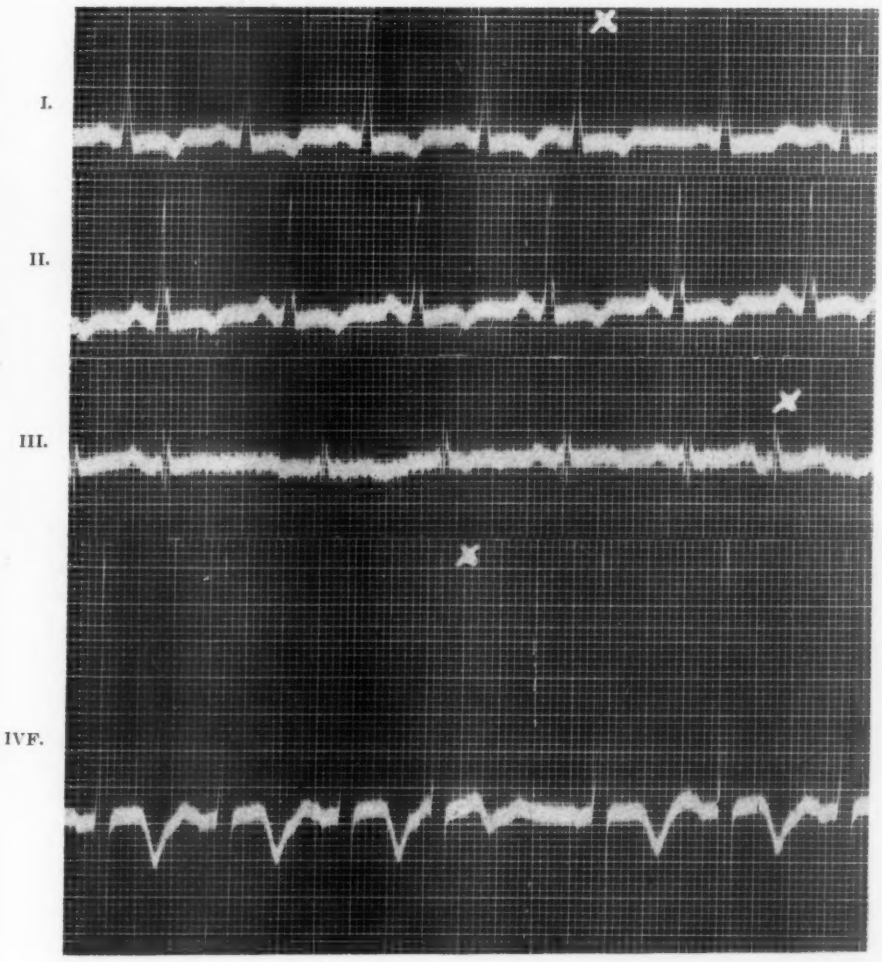


Fig. 5.—A four-lead electrocardiogram. Little aberration of the APS in the limb leads, definite aberration in the chest lead.

either amplitude, duration, or configuration, and called the group "first degree aberration." There were 179 types in this group. The group "second degree aberration" (Fig. 7), which was characterized by two changes, namely, amplitude *and* configuration, comprised 86 types. The next group, "third degree aberration" (Fig. 8), with a combination of three changes, namely, amplitude, configuration, and direction, was still

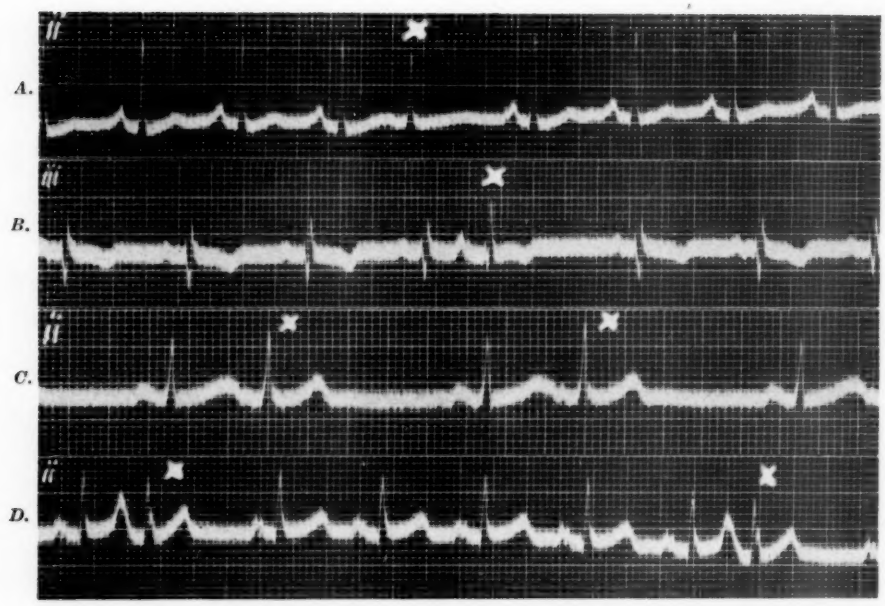


Fig. 6.—First and second degree aberration of APS (four cases). *A*, Change in amplitude of QRS (first degree aberration). *B*, Change in direction of QRS, here accompanied by a change in configuration (second degree aberration): *C*, Change in duration of QRS (first degree aberration). *D*, Change in configuration of QRS (first degree aberration).

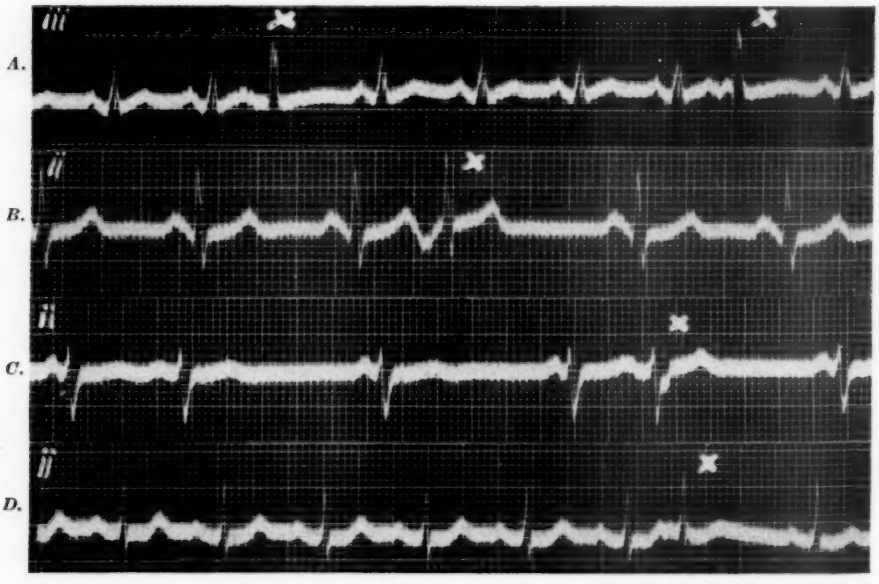


Fig. 7.—Second degree aberration of APS (four cases). *A*, Change in amplitude and configuration of QRS. *B*, Change in amplitude and duration of QRS. *C*, Change in duration and configuration of QRS. *D*, Change in configuration of QRS; besides, R is of higher, S of lower, amplitude.

smaller (45 types), and the group "fourth degree aberration" (Figs. 9 and 10) was the smallest of all, consisting of only 28 types. This group was in many ways the most interesting. In these APS, the amplitude, duration, configuration, and direction of QRS were different from those of the normal beats. Aberration of the T wave, as a rule, was correspondingly marked, although reversal of the direction of T was seen only twice. The QRS complexes of this group are likely to be as wide and notched as those of bundle branch block. Compared to the QRS complexes of the normal beats, they often appear so bizarre that

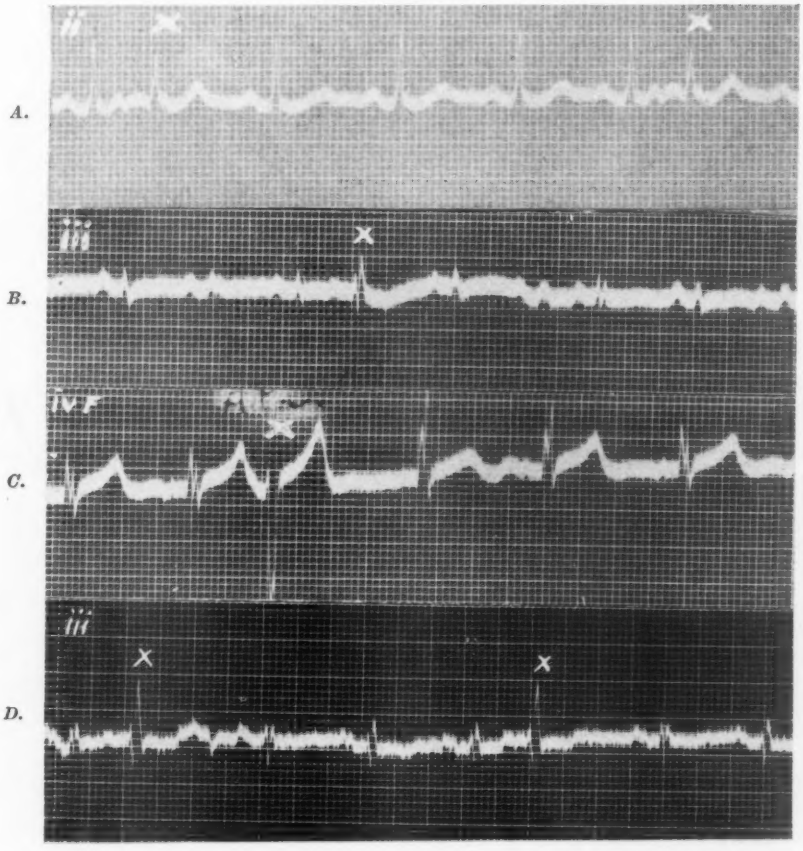


Fig. 8.—Third degree aberration of APS (four cases). *A*, *B*, and *D*, Change in amplitude, duration, and configuration of QRS. *C*, Change in amplitude, direction, and configuration of QRS.

the APS are commonly mistaken for premature systoles of ventricular origin. These QRS complexes are, of course, preceded by abnormal premature P waves. In all but two instances, however, the APS with "fourth degree aberration" occurred so early in diastole that their P waves were superimposed on the preceding T waves, on either the downstroke or the upstroke. Such inconspicuousness of the P waves (Fig.

10) increases the likelihood that these APS may be mistaken for ventricular premature systoles (VPS).* The distinction between such APS and VPS may be of more than academic importance. For one thing, the patient may be receiving digitalis, and the mistaken interpretation of the bizarre APS for VPS may lead to the suspicion of toxic digitalis effect. That suspicion would not arise if the auricular origin of the bizarre premature systoles were recognized, for digitalis does not cause APS. A second, and equally serious error may result if bizarre APS coexist with VPS. In that case, a bizarre APS may simulate a VPS arising from a different focus. Since multifocal VPS indicate myocardial damage, the misinterpretation may lead to a wrong diagnosis (Fig. 10).

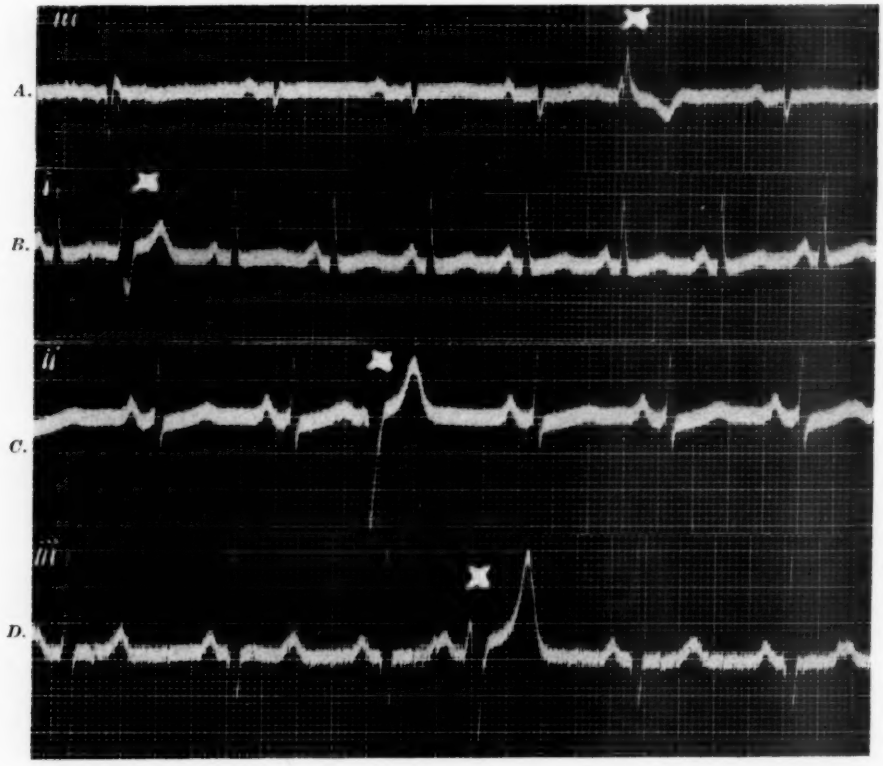


Fig. 9.—Fourth degree aberration of APS (four cases). All four characteristics of QRS are changed. Such bizarre APS are likely to be mistaken for VPS.

Conflicting Opinions on the Cause of Aberration.—The cause of aberration is still obscure, and the literature contains conflicting statements regarding its mechanism. It seems an established fact that the change in the QRS complex depends upon abnormal spreading of the contraction. Lewis[1] states: "The changed form of the ventricular

*VPS will be used as an abbreviation for ventricular premature systole throughout the remainder of this paper.

complex is due, so it is maintained, to defects in conduction through some of the chief Purkinje strands," and he finds it "notable that in these patients minor defects in the main bundle are the rule." On another occasion, Lewis[2] states: "Auricular extrasystoles showing aberrant ventricular complexes are almost confined to hearts in which

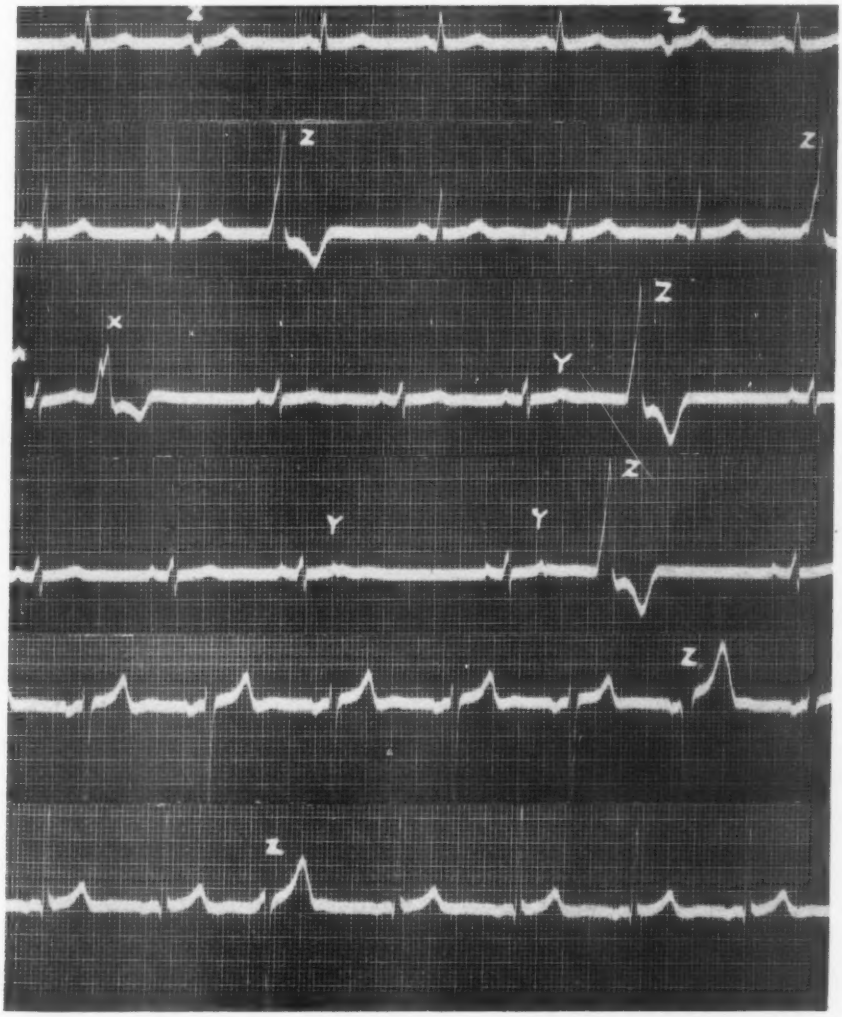


Fig. 10.—Erroneous diagnosis of myocardial damage caused by misinterpretation of an APS. *x*, APS; *y*, blocked APS; *z*, VPS. *x* (in Lead III) is preceded by an inconspicuous P wave which is superimposed on the preceding T wave. The ventricular complex of *x* is bizarre. *x* was, therefore, misinterpreted as a VPS by one examiner. The diagnosis of "myocardial damage" was then based on the finding of "multifocal VPS." Yet apart from the arrhythmia and the notching of P in Lead II, this electrocardiogram is probably within normal limits.

conduction defects in the junctional tissues are demonstrable." Pardee[6] disagrees with Lewis, and finds it hard to believe "that all patients who have premature auricular contractions have either an abnormality of function or structural disease in the A-V conduction system;" he

ascribes aberration to asynchronous stimulation of the ventricles resulting from the abnormal way in which the impulse reaches and leaves the A-V node. Wenckebach and Winterberg[7] also raise the question whether "the more pronounced disturbances of this type, particularly abnormal intraventricular conduction in APS, are not of more than mere functional significance, and whether they might not indicate disease of the conduction system." Wenckebach, however, answers his own question in the negative, and other authors [Katz,[8] Pardee,[6] and White[3]] do likewise. Carter[5] and Bellet and McMillan,[10] on the other hand, follow Lewis' trend and ascribe definite pathologic significance to the phenomenon of aberration.

Faced with such conflicting statements regarding the significance of aberration in man, we turn to reports on animal experiments, but there, too, we find contradictions. Pardee[6] states that aberrant ventricular complexes are common in normal dogs with artificially induced premature auricular contractions; he considers it difficult to find a reason why there should be a localized abnormality of the auriculoventricular conduction system in normal dogs, even when they are under an anesthetic. Stenstroem,[11] on the other hand, who worked on rabbits, never found the ventricular complexes of artificially produced APS aberrant as long as the hearts were intact. Stenstroem furnished weighty experimental evidence to indicate that aberration is due to impaired conduction through the bundle branches. He invented an apparatus which produces premature systoles by electrical stimulation. Before stimulating the auricles, Stenstroem exerted pressure on those parts of the interventricular septum through which the branches of His' bundle pass, and temporarily injured one of the branches. He waited until the electrocardiogram returned to normal, and then produced APS. These APS showed constant aberration; when the left bundle branch was injured, their ventricular complexes took on the shape of the dextrocardiogram; when the right bundle branch was injured, their ventricular complexes took on the shape of the levocardiogram; and when both bundle branches were injured simultaneously, the ventricular complexes of the APS took on the shape of either the levocardiogram or the dextrocardiogram.

Convincing experimental evidence, such as that of Stenstroem, strengthened us in the belief that, in man, aberration of the ventricular complexes of APS might at times also be indicative of a pathologic condition of the conducting tissues. We decided to investigate the problem in two ways, namely, by electrocardiographic analysis and by correlation of electrocardiographic and clinical observations.

It has often been stated that aberration is usually more marked in those APS which are very premature, and a causal connection between prematurity and aberration has long been assumed. Lewis[1] was the first to note that "the ventricular complex diverges from normal most con-

TABLE II

RELATIVE FREQUENCY OF THE DIFFERENT DEGREES OF PREMATURITY OF AURICULAR PREMATURE SYSTOLES (APS)

LATE APS (LOCATION I): THE P WAVE OF THE APS DOES NOT TOUCH THE T WAVE OF THE PRECEDING BEAT	FAIRLY LATE APS (LOCATION II): THE P WAVE OF THE APS BARELY TOUCHES THE DESCENDING LIMB OF THE T WAVE OF THE PRECEDING BEAT	MODERATELY EARLY APS (LOCATION III): THE P WAVE OF THE APS IS SUPERIMPOSED ON THE DESCENDING LIMB OF THE PRECEDING T WAVE	EARLY APS (LOCATION IV): THE P WAVE OF THE APS IS SUPERIMPOSED ON THE ASCENDING LIMB OF THE PRECEDING T WAVE	VERY EARLY APS (LOCATION V): THE P WAVE OF THE APS IS SUPERIMPOSED ON THE PRECEDING RS-T SEGMENT CLOSE TO THE QRS COMPLEX	TOTAL
101	138	180	100	6	525

TABLE III

NUMBER OF DIFFERENT TYPES OF AURICULAR PREMATURE SYSTOLES (APS) PER CASE

NUMBER OF DIFFERENT TYPES OF APS PER CASE	ONE	TWO	THREE	FOUR	FIVE	SIX AND MORE	TOTAL
NUMBER OF CASES	52	51	51	27	11	9	201

spicuously when the extrasystole falls early in diastole; in some patients aberration is closely related to the degree of prematurity.'' Lewis, who attributes the aberration to deficient conduction along certain tracts of the junctional tissues, explains that ''the deficiency has been confined to the premature beats *because the rest preceding these* has been brief.''[2] Other authors, namely, Katz,[8] and Scherf and Boyd[9] express the opinion that prematurity is the only cause of aberration. Stenstroem,[11] however, referring to APS in a human subject, reported that ''the extent of aberration was *not* entirely determined by the elapse of time between a normal complex and its following extrasystole.''

Prematurity and Aberration.—We analyzed our own electrocardiographic material in order to learn whether prematurity was the sole factor determining the degree of aberration. Our results are summarized in Table IV. A number of observations demonstrated the marked influence of prematurity on aberration.

1. We found 24 patients with APS showing ''fourth degree'' aberration; the abberation affected amplitude, duration, direction, and configuration of the QRS complex, and the APS had a bizarre appearance. Four of the 24 patients exhibited bizarre APS of two different degrees of prematurity; there were, therefore, 28 different ''types'' of such bizarre APS. None of the 28 occurred late in diastole (Table V). All except two occurred early in diastole, and the two which occurred ''fairly late in diastole'' (Location II) were associated with slow heart rates (which lengthen diastole).

2. Contrariwise, there were 28 patients with APS which never showed any aberration of either QRS or T. Six of these patients exhibited APS

TABLE IV

INFLUENCE OF PREMATURITY ON ABERRATION

DEGREE OF PREMATURITY	NUMBER OF TYPES	BLOCKED	NO ABERRATION AT ALL	ABERRATION OF T ONLY	QRS CHANGED IN AMPLITUDE ONLY	QRS CHANGED IN DIRECTION ONLY	QRS CHANGED IN DURATION ONLY	QRS CHANGED IN CONFIGURATION ONLY	R TALLER, S SMALLER, OR VICE VERSA	R THE SAME, S DEEPER OR S THE SAME, R TALLER	DIFFERENCE IN SIZE OF Q ONLY	SECOND DEGREE ABERRATION	THIRD DEGREE ABERRATION	FOURTH DEGREE ABERRATION
Late APS (Location I)	101	0	50	15	9	0	2	13	5	1	1	5	0	0
Fairly late APS (Location II)	138	0	33	11	29	0	3	12	16	0	4	20	7	3
Moderately early APS (location III)	180	3	45	10	25	0	2	12	11	1	8	33	18	12
Early APS (Location IV)	100	5	11	5	16	0	3	5	2	0	1	24	17	11
Very early APS (Location V)	6	0	0	0	0	0	0	0	0	0	0	1	3	2
All types	525	8	139	41	79	0	10	42	34	2	14	83	45	28

TABLE V

AURICULAR PREMATURE SYSTOLES (APS) WITH MARKED ABERRATION, AND APS WITHOUT ANY ABERRATION—THEIR LOCATION IN DIASTOLE

	NUMBER OF CASES	NUMBER OF DIFFERENT APS	LOCATION I (LATE IN DIASTOLE)	LOCATION II (FAIRLY LATE IN DIASTOLE)	LOCATION III (MODERATELY EARLY IN DIASTOLE)	LOCATION IV (EARLY IN DIASTOLE)	LOCATION V (VERY EARLY IN DIASTOLE)
Marked (fourth degree) aberration; bizarre ventricular complexes	24	28	0	3	12	11	2
No aberration at all	28	35	20	6	7	2	0

of two or more different degrees of prematurity; there was, therefore, a total of 35 different "types" of APS without any aberration whatever. The majority of these (Table V) occurred late in diastole, and none occurred very early in diastole.

3. We then approached the problem from the opposite side, and grouped our 525 types of APS according to the degree of their prematurity (their location in diastole). The data of this analysis (Table IV) furnish convincing evidence that prematurity influences abberration: none of the 101 APS occurring late in diastole (our "Location I") ever showed the higher degrees of aberration. Conversely, none of the six tyes of APS occurring very early in diastole were free from aberration.

TABLE VI

RELATIONSHIP OF PREMATURITY AND ABERRATION IN 149 CASES SHOWING MULTIPLE TYPES OF APS

ABERRATION INCREASES WITH INCREASING PREMATURITY	ABERRATION DECREASES WITH INCREASING PREMATURITY	SAME DEGREE OF PREMATURITY, BUT DIFFERENT DEGREE OF ABERRATION	SAME ABERRATION, BUT DIFFERENT DEGREE OF PREMATURITY	COMBINATION I: ABERRATION INCREASES WITH INCREASING PREMATURITY IN SOME INSTANCES; SAME DEGREE OF PREMATURITY, DIFFERENT DEGREE OF ABERRATION IN OTHERS	COMBINATION II: ABERRATION DECREASES WITH INCREASING PREMATURITY IN SOME INSTANCES; SAME DEGREE OF PREMATURITY, DIFFERENT DEGREE OF ABERRATION IN OTHERS	TOTAL
16	12	48	11	27	35	149

Were we to judge only by the observations so far mentioned, it might seem that prematurity alone determines the occurrence and the degree of aberration. Other observations of ours, however, do not support that conclusion. In the first place, there were too many exceptions to the rule. Marked prematurity was not necessarily associated with abberation; it actually occurred without it (Table V). There were, for instance, 100 types of early APS (Location IV); 11 of these showed no aberration at all, and five more showed aberration of the T wave or the S-T segment without aberration of QRS (Table IV). In the second place, the many electrocardiograms with several different types of APS in the same record or the same lead showed that different influences were at work; often there was no parallelism between prematurity and aberration. Table VI illustrates this point. In 149 of our 201 cases, multiple types of APS were present, but in only a *small* minority, 16, did aberration increase with increasing prematurity (Fig. 11, *A*); in 12 cases, aberration actually decreased with increasing prematurity (Fig. 11, *B*). The great majority of the 149 cases, however, did not fit in either of these groups. They exhibited three or more different types of APS: in some instances, aberration increased with increasing prematurity in two types, but not in the third; in other instances, other combinations occurred; the various combinations are summarized in Table VI. The entire group of 149 cases of multiple APS included 51 cases with only two types of APS. If we analyze this smaller group alone, we obtain a much clearer picture (Table VII). It is then clear that the degree of prematurity and the degree of aberration are usually not parallel. In only ten of the 51 cases did aberration increase with increasing prematurity; in seven cases it decreased. The remainder of the cases, 34, fell into two groups. In one group, abberation differed even though the degree of prematurity was the same (24 cases) (Fig. 11, *D*); in the other group, prematurity varied while the degree of aberration remained the same (ten cases) (Fig. 11, *C*). From these figures, the lack of a consistent relationship between aberration and prematurity is apparent. We are, therefore, led to the conclusion that prematurity is *not* the sole factor which determines the degree of aberration. In an effort to find other determining factors we then investigated the possible influence of the frequency of the APS and the P-R interval of the APS.

Effect of Frequency of APS on Their Aberration.—Stenstroem[11] reported that the frequency of theAPS influences their aberration. We

TABLE VII

ABERRATION IN THE PRESENCE OF TWO DIFFERENT TYPES OF APS

ABERRATION INCREASES WITH PREMATURITY	ABERRATION DECREASES WITH PREMATURITY	ABERRATION SAME, LOCATION DIFFERENT	LOCATION SAME, ABERRATION DIFFERENT	TOTAL NUMBER OF CASES
10	7	10	24	51

grouped our cases according to the total number of APS found in each electrocardiogram, and compared the occurrence of the different degrees of aberration in the different frequency groups (Table VIII). Contrasting only the extremes, we did indeed find a difference between cases with only a single APS and those with 21 or more in one record; half (48.3 per cent) of the APS which occurred singly showed no aberration at all, whereas abberation, especially of the higher degrees, was

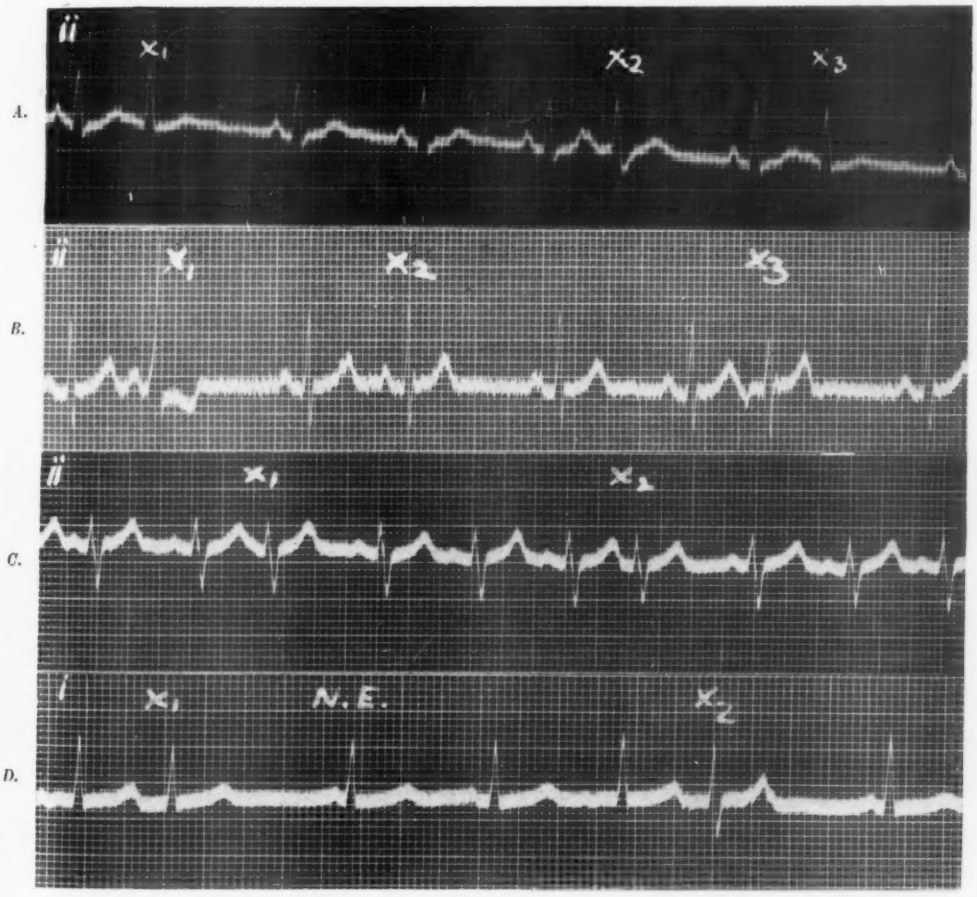


Fig. 11.—Multiple APS, showing the varying relationship between aberration and the degree of prematurity. *A*, Aberration increases with increasing prematurity. x_1 and x_3, APS of Location III, show first degree aberration; x_2, APS of Location IV, shows second degree aberration. *B*, Aberration decreases with increasing prematurity. x_1, APS of Location II, shows third degree aberration; x_3, APS of Location III, shows first degree aberration. *C*, Aberration the same, location varies. x_2 is more premature than x_1, yet shows no more aberration. *D*, Location the same, aberration varies. x_1 and x_2 both have Location III, yet x_2 shows more aberration than x_1.

frequent in records containing a multitude of APS. The relationship, however, became much less definite when records showing a moderate number of APS per tracing were analyzed, and such records were more numerous. Records with two to five APS per tracing, for instance,

TABLE VIII

ABERRATION OF AURICULAR PREMATURE SYSTOLES (APS) CORRELATED WITH THEIR FREQUENCY

NUMBER OF APS PER ELECTRO-CARDIO-GRAM	NO ABERRA-TION AT ALL	MAXIMAL ABERRATION					TOTAL NUMBER OF CASES
		ABERRA-TION OF T WAVE ONLY	FIRST DEGREE ABERRA-TION OF QRS	SECOND DEGREE ABERRA-TION OF QRS	THIRD DEGREE ABERRA-TION OF QRS	FOURTH DEGREE ABERRA-TION OF QRS	
1	14 (48.3%)	0	7 (24.1%)	4 (13.7%)	3 (10.3%)	1 (3.4%)	29
2 to 5	21 (23.1%)	3 (3.3%)	31 (34.1%)	20 (22.0%)	9 (9.9%)	7 (7.7%)	91
6 to 10	6 (13.9%)	1 (2.3%)	10 (23.3%)	16 (37.1%)	4 (9.3%)	6 (13.9%)	43
11 to 20	3 (10.0%)	1 (3.3%)	9 (30.0%)	5 (16.7%)	4 (13.3%)	8 (26.7%)	30
21 to 30	1 (14.3%)	0	1 (14.3%)	2 (28.6%)	1 (14.3%)	2 (28.6%)	7
31 and over	0	0	0	1 (100.0%)	0	0	1
	45	5	58	48	21	24	201

showed a fairly even distribution of the different degrees of aberration, and absence of aberration was about as frequent as "second degree" aberration. The highest degrees of aberration, in general, are infrequent; they, therefore, could not be expected to be numerous in this group. In any event, it should be remembered that the number of cases available for analysis was small, and that the findings were equivocal. We felt justified in concluding that no definite relationship exists between the frequency of APS and the aberration of their ventricular complexes.

P-R Interval and Aberration.—We occasionally encountered two types of APS in the same record which differed greatly in the duration of their P-R intervals, and it occurred to us that the difference in aberration might depend on the difference in the P-R intervals; the APS with a long P-R interval might possibly show marked aberration, and the APS with a short P-R interval might possibly be free from aberration. To investigate the relationship, we again used our two extreme groups, APS without any aberration, and APS with marked aberration. In both groups (Table IX) we found APS with P-R intervals longer than

TABLE IX

P-R INTERVALS OF AURICULAR PREMATURE SYSTOLES (APS) WITHOUT ABERRATION, AND OF APS WITH MARKED ABERRATION

	NUMBER OF CASES	P-R INTERVAL RELATIVELY PROLONGED	P-R INTERVAL RELATIVELY SHORTENED	P-R INTERVAL THE SAME AS THAT OF NORMAL BEATS
APS without aberration	28	8 (29.5%)	12 (41.0%)	8 (29.5%)
APS with marked (fourth degree) aberration	24	13 (52.2%)	8 (34.8%)	3 (13.0%)

those of the normal beats, and APS with shorter P-R intervals. There were more instances of relative P-R interval prolongation among APS with marked aberration than among those without aberration. The preponderance, however, was not striking; probably it was incidental and due to greater frequency of A-V conduction disturbances in this group. Negative results were also obtained when we approached the problem from the opposite side. We collected all APS with abnormally prolonged P-R intervals and all APS with very short P-R intervals, and compared the incidence of aberration in both groups; there was no significant difference (Table X). We concluded, therefore, that P-R interval changes in APS have no demonstrable influence on the aberration of their ventricular complexes.

TABLE X

OCCURRENCE OF ABERRATION IN AURICULAR PREMATURE SYSTOLES (APS) WITH PROLONGED P-R INTERVALS AND APS WITH SHORT P-R INTERVALS

	NUMBER OF CASES	NO ABERRATION	FIRST DEGREE ABERRATION	SECOND DEGREE ABERRATION	THIRD DEGREE ABERRATION	FOURTH DEGREE ABERRATION
APS with abnormally prolonged P-R intervals	12	7	2	0	0	3
APS with short P-R intervals	20	8	8	4	0	0

Correlation of Clinical and Electrocardiographic Observations.—The electrocardiographic part of our investigation was thus concluded. It had shown that the degree of prematurity of APS had an influence on the aberration of their ventricular complexes, but that it was not the only determining factor. Our results had strongly suggested that other factors might be operative. The clinical part of our study was essentially a search for these other factors. Our aim was to investigate the influence of pathologic conditions on aberration. In this effort, we were encouraged by Stenstroem's[11] experiments on rabbits, previously described, for we regarded it as probable that Stenstroem's conclusions applied to human hearts as well.

In our clinical study, we analyzed the charts of the 201 patients and, in each case, carefully noted the diagnosis, as well as the significant findings on which it was based. A large number of the patients were examined by us personally. In cardiac patients, special note was made of the presence or absence of congestive heart failure and its objective signs. When changes in the cardiac status occurred, they were noted. Whenever a patient received a drug known to affect the electrocardiogram, for instance, digitalis or quinidine, the fact was recorded. Note was also made of the patient's age, blood pressure, and all roentgenologic and laboratory data.

TABLE XI

CORRELATION OF AGE AND DEGREE OF ABERRATION

	NO ABERRATION AT ALL	FOURTH DEGREE ABERRATION
Number of cases	28	24
Average age (yrs.)	56½	55

Age Factor.—We studied the age factor first. A pathologic condition of the conduction system, we thought, was more likely to be present in older patients. We first noted the ages of all patients (24) with "fourth degree aberration," and then, by way of contrast, the ages of all patients (28) whose APS showed no aberration at all (Table XI). In the latter group, the average age was 56½ years, and, in the former, it was 55 years; the difference was obviously insignificant. We then grouped all our patients according to age, and found that marked aberration was no more frequent among the aged than among the young. We also observed marked aberration in children. Conversely, we found APS without any aberration in the electrocardiograms of several patients over 70 years of age. Our analysis of the age distribution, therefore, failed to give us a clue to the "missing factor."

Aberration in Cardiac and Noncardiac Patients.—We divided our patients into three groups, according to diagnosis: 29 noncardiac patients, 103 cardiac patients without congestive heart failure, and 63 cardiac patients with congestive heart failure (Table XII). Six cases were ex-

TABLE XII

CORRELATION OF CARDIAC STATUS AND DEGREE OF ABERRATION

	NONCARDIAC PATIENTS	CARDIAC PATIENTS WITHOUT SIGNS OF CONGESTIVE HEART FAILURE	CARDIAC PATIENTS WITH CONGESTIVE HEART FAILURE	EXCLUDED FROM ANALYSIS BECAUSE OF INADEQUATE DIAGNOSTIC STUDY
NUMBER OF CASES	29	103	63	6
ABERRATION VARIED FROM	None to fourth degree aberration	None to fourth degree aberration	None to fourth degree aberration	None to second degree aberration
NUMBER OF CASES IN WHICH NO ABERRATION OCCURRED	4	15	7	2
NUMBER OF CASES IN WHICH FOURTH DEGREE ABERRATION OCCURRED	2	15	7	0
PREMATURITY VARIED FROM	Location I to Location V	Location I to Location IV	Location I to Location V	Location I to Location IV

TABLE XIII

AURICULAR PREMATURE SYSTOLES (APS) IN NONCARDIAC PATIENTS

CASE	AGE (YRS.)	DIAGNOSIS	DEGREE OF PREMATURITY	MAXIMUM DEGREE OF ABERRATION
1	12	Lobar pneumonia	Locations I & II	First degree
2	45	Lobar pneumonia	Locations IV & V	Third degree
3	34	Lymphogranuloma venereum	Location I	Aberration of T only
4	28	Infectious arthritis	Location IV	Second degree
5	39	Subdeltoid bursitis	Location I	First degree
6	42	Cystocele	Locations II & III	Second degree
7	17	Psychoneurosis	Location II	First degree
8	23	Pulmonary embolization following cesarean section	Location IV	Blocked APS
9	34	Cholecystitis	Location III	First degree
10	14	Tonsillitis	Location II	No aberration
11	12	Bronchopneumonia	Location III	Fourth degree
12	58	Pernicious anemia	Location II	First degree
13	70	Carcinoma of lung	Location IV	First degree
14	9	Cervical lymphadenitis	Location I	First degree
15	31	Lobar pneumonia	Location II	First degree
16	48	Fracture of skull	Location II	Second degree
17	58	Bronchopneumonia	Locations III & IV	First degree
18	38	Bronchial asthma	Location II	Second degree
19	2	Lobar pneumonia	Location I	No aberration
20	19	Bronchial asthma	Location II	Third degree
21	36	Gonorrheal arthritis	Location III	Third degree
22	21	Healthy adult	Location III	First degree
23	27	Cellulitis of face	Location III	Second degree
24	53	Healthy adult	Location I	No aberration
25	53	Bronchial asthma	Location IV	Fourth degree
26	44	Tuberculous lymphadenitis	Location IV	Blocked APS
27	79	Adenocarcinoma of colon	Location IV	Second degree
28	48	Hodgkin's disease	Location III	First degree
29	23	Thrombosis of cerebral artery	Location I	No aberration

cluded because of inadequate diagnostic study. We then attempted to correlate the cardiac status of the patients with the degree of aberration. The results were disappointing; there was little difference among the three groups. In the noncardiac group (Table XIII), all degrees of aberration occurred, including "fourth degree aberration" with bizarre ventricular complexes (two cases). Absence of aberration occurred only four times. The distribution was not significantly different from that in the two cardiac groups. In these also, all degrees of aberration occurred, and, remarkably enough, complete absence of aberration was found quite frequently, i.e., fifteen times among the 103 cardiac patients without congestive heart failure, and seven times among the 63 cardiac patients with congestive heart failure. Several patients of the last group were very ill; some were suffering from acute myocardial infarction, and others, from pulmonary infarction, but their electrocardiograms otherwise thoroughly abnormal, showed APS without aberration. The electrocardiogram of a moribund patient which showed left bundle branch block also showed APS without any aberration. Absence of aberration was common in normal and abnormal electrocardiograms alike. Our conclusion was that neither the presence nor the absence of heart

TABLE XI

CORRELATION OF AGE AND DEGREE OF ABERRATION

	NO ABERRATION AT ALL	FOURTH DEGREE ABERRATION
Number of cases	28	24
Average age (yrs.)	56½	55

Age Factor.—We studied the age factor first. A pathologic condition of the conduction system, we thought, was more likely to be present in older patients. We first noted the ages of all patients (24) with "fourth degree aberration," and then, by way of contrast, the ages of all patients (28) whose APS showed no aberration at all (Table XI). In the latter group, the average age was 56½ years, and, in the former, it was 55 years; the difference was obviously insignificant. We then grouped all our patients according to age, and found that marked aberration was no more frequent among the aged than among the young. We also observed marked aberration in children. Conversely, we found APS without any aberration in the electrocardiograms of several patients over 70 years of age. Our analysis of the age distribution, therefore, failed to give us a clue to the "missing factor."

Aberration in Cardiac and Noncardiac Patients.—We divided our patients into three groups, according to diagnosis: 29 noncardiac patients, 103 cardiac patients without congestive heart failure, and 63 cardiac patients with congestive heart failure (Table XII). Six cases were ex-

TABLE XII

CORRELATION OF CARDIAC STATUS AND DEGREE OF ABERRATION

	NONCARDIAC PATIENTS	CARDIAC PATIENTS WITHOUT SIGNS OF CONGESTIVE HEART FAILURE	CARDIAC PATIENTS WITH CONGESTIVE HEART FAILURE	EXCLUDED FROM ANALYSIS BECAUSE OF INADEQUATE DIAGNOSTIC STUDY
NUMBER OF CASES	29	103	63	6
ABERRATION VARIED FROM	None to fourth degree aberration	None to fourth degree aberration	None to fourth degree aberration	None to second degree aberration
NUMBER OF CASES IN WHICH NO ABERRATION OCCURRED	4	15	7	2
NUMBER OF CASES IN WHICH FOURTH DEGREE ABERRATION OCCURRED	2	15	7	0
PREMATURITY VARIED FROM	Location I to Location V	Location I to Location IV	Location I to Location V	Location I to Location IV

TABLE XIII

AURICULAR PREMATURE SYSTOLES (APS) IN NONCARDIAC PATIENTS

CASE	AGE (YRS.)	DIAGNOSIS	DEGREE OF PREMATURITY	MAXIMUM DEGREE OF ABERRATION
1	12	Lobar pneumonia	Locations I & II	First degree
2	45	Lobar pneumonia	Locations IV & V	Third degree
3	34	Lymphogranuloma venereum	Location I	Aberration of T only
4	28	Infectious arthritis	Location IV	Second degree
5	39	Subdeltoid bursitis	Location I	First degree
6	42	Cystocele	Locations II & III	Second degree
7	17	Psychoneurosis	Location II	First degree
8	23	Pulmonary embolization following cesarean section	Location IV	Blocked APS
9	34	Cholecystitis	Location III	First degree
10	14	Tonsillitis	Location II	No aberration
11	12	Bronchopneumonia	Location III	Fourth degree
12	58	Pernicious anemia	Location II	First degree
13	70	Carcinoma of lung	Location IV	First degree
14	9	Cervical lymphadenitis	Location I	First degree
15	31	Lobar pneumonia	Location II	First degree
16	48	Fracture of skull	Location II	Second degree
17	58	Bronchopneumonia	Locations III & IV	First degree
18	38	Bronchial asthma	Location II	Second degree
19	2	Lobar pneumonia	Location I	No aberration
20	19	Bronchial asthma	Location II	Third degree
21	36	Gonorrheal arthritis	Location III	Third degree
22	21	Healthy adult	Location III	First degree
23	27	Cellulitis of face	Location III	Second degree
24	53	Healthy adult	Location I	No aberration
25	53	Bronchial asthma	Location IV	Fourth degree
26	44	Tuberculous lymphadenitis	Location IV	Blocked APS
27	79	Adenocarcinoma of colon	Location IV	Second degree
28	48	Hodgkin's disease	Location III	First degree
29	23	Thrombosis of cerebral artery	Location I	No aberration

cluded because of inadequate diagnostic study. We then attempted to correlate the cardiac status of the patients with the degree of aberration. The results were disappointing; there was little difference among the three groups. In the noncardiac group (Table XIII), all degrees of aberration occurred, including "fourth degree aberration" with bizarre ventricular complexes (two cases). Absence of aberration occurred only four times. The distribution was not significantly different from that in the two cardiac groups. In these also, all degrees of aberration occurred, and, remarkably enough, complete absence of aberration was found quite frequently, i.e., fifteen times among the 103 cardiac patients without congestive heart failure, and seven times among the 63 cardiac patients with congestive heart failure. Several patients of the last group were very ill; some were suffering from acute myocardial infarction, and others, from pulmonary infarction, but their electrocardiograms otherwise thoroughly abnormal, showed APS without aberration. The electrocardiogram of a moribund patient which showed left bundle branch block also showed APS without any aberration. Absence of aberration was common in normal and abnormal electrocardiograms alike. Our conclusion was that neither the presence nor the absence of heart

failure nor other features of the cardiac status had any influence on aberration.* It may be argued that the number of patients in each group was too small, that diagnostic errors could not always be tracked down, and that necropsy findings were available in very few cases. We doubt whether our results would have been different, had the number of patients and necropsies been greater. We believe that our conclusion is valid because our analysis did not give the slightest hint of a relationship between cardiac status and aberration.

Change of Aberration in Serial Electrocardiograms.—Our results, so far, had been uniformly negative, but we approached the problem from still another angle, and this approach proved more successful. We studied serial electrocardiograms of patients who repeatedly exhibited APS, and searched these records for variations in the degree of aberration. As a rule, the configuration of APS did not change, even over long periods, provided they arose in the same focus and the degree of their prematurity was the same. In certain instances, however, the degree of aberration did change, and these were the records we used for correlation. We compared the clinical condition of these patients at the time of their first electrocardiogram with the condition at the time of subsequent tracings, and found that the change in aberration corresponded to a change in the clinical condition. This observation, for the first time, suggested that aberration is a finding of clinical significance. To illustrate this point, three characteristic cases will now be reported.

CASE REPORTS

CASE 1.—F. K., aged 31 years, admission No. 21241, was admitted to the hospital March 14, 1932, with the typical signs of lobar pneumonia in the left lower lobe. On March 15, 1932, the patient was profoundly toxic; the temperature was 105° F., and the leucocyte count was 42,500. The electrocardiogram taken on that day showed evidence of myocardial impairment (low amplitude of the T waves in Lead II). Numerous APS were present, and their QRS-T complexes, especially in Lead III (Fig. 12, *A*) showed aberration (lower amplitude of QRS, duration of QRS, decreased from 0.08 to 0.07 second, notching of the R wave near its tip, absence of the S wave, elevation of the RS-T junction, and increased inversion of the T wave). On April 6, 1932, when the patient had been afebrile and convalescent for twelve days, a second electrocardiogram was taken (Fig. 12, *B*). It showed no more evidence of myocardial damage (the T waves in Lead II were now of normal amplitude). The APS of this electrocardiogram, which arose in the same focus as those of March 15, 1932, showed only minimal aberration of the QRS complexes (lower amplitude of R, slightly decreased duration of QRS) and very little aberration of the T waves. The change from marked to minimal aberration in this case was quite remarkable. No drugs known to affect the electrocardiogram had been given to the patient. We are inclined, there-

*In this connection another observation may be mentioned. The APS of the noncardiac patients showed all degrees of prematurity. They did not differ from those of the two cardiac groups in that respect, either.

fore, to ascribe the decrease in aberration to the improvement of the clinical condition. It seems very probable to us that the severe pneumonia had been a cause of the aberration.

CASE 2.—S. R., aged 70 years, admission No. 70366, a case of hypertensive heart disease of at least ten years' duration, was admitted to the hospital Dec. 4, 1941, acutely ill with pneumonia in the left lower lobe. On admission, premature beats were heard, but no electrocardiogram was taken. The pneumonic process responded promptly to treatment with sulfadiazine, and the temperature, which had been 101.8° F., became normal within three days. On Dec. 20, 1941, the patient's convalescence was interrupted by an attack of acute left ventricular failure which was assumed to be secondary to myocardial infarction; her temperature, on that day, rose to 103° F. An electrocardiogram taken the following day (Fig. 13) showed numerous APS and evidence of myocardial damage (low voltage and slurring of the QRS complexes in the standard leads, with a broad Q wave in Lead I, depression of the RS-T segment in Leads I and IVF, diphasic T waves in Leads I and IVF, and low amplitude of the T waves in Lead II). The patient then received 1.8 Gm. of quinidine sulfate within two days. On Dec. 23, 1941, she suffered a left-sided hemiparesis, presumably due to a

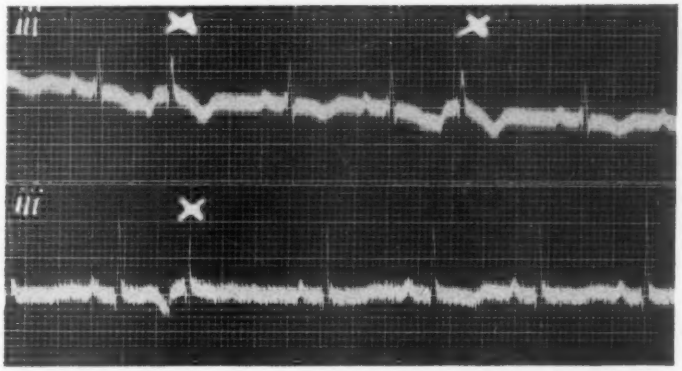


Fig. 12.—Case 1. Change in aberration during the course of severe pneumonia. *A*, Record taken March 15, 1932 (only Lead III is shown) shows two APS (*x*, *x*), with fairly marked aberration (QRS of lower amplitude, QRS duration decreased from 0.08 to 0.07 second, notching of the R wave near its tip, absence of the S wave, elevation of the RS-T junction, increased inversion of the T wave). The patient, on that day, was profoundly toxic, with a temperature of 105°F. and a leucocyte count of 42,500. *B*, Record taken April 6, 1932 (only Lead III is shown) shows one APS (*x*) with slight aberration (QRS of lower amplitude, slight elevation of RS-T junction). The patient, on that day, was afebrile and convalescing.

cerebral embolus; her cardiac condition remained grave. A second electrocardiogram was taken on that day (Fig. 14); it differed from the first in several points: higher amplitude of T_2 and T_3, prolongation of the Q-T interval from 0.35 second to 0.42 second, and, what is of greatest interest here, a higher degree of aberration of the APS. In the earlier tracings, the APS showed no aberration of QRS and minimal aberration of the T waves. In the second record, however, the APS showed QRS complexes which differed from those of the normal beats in three features (change in amplitude, best seen in Lead III, change in duration, best seen in Lead II, and change in configuration, best seen in Lead IVF). The patient died Dec. 24, 1941; permission for

necropsy was not obtained. The two electrocardiograms were taken at an interval of only two days, yet the difference in aberration was striking. Two explanations for this difference seem possible. On the day before the patient's death, her myocardium may have deteriorated, and a pathologic condition of the conduction system may have developed which manifested itself in increased aberration of the APS; or quinidine may have affected the conduction system. The second explanation seems more plausible in view of the other evidence of quinidine effect (prolongation of Q-T), and in view of the facts learned from the next case.

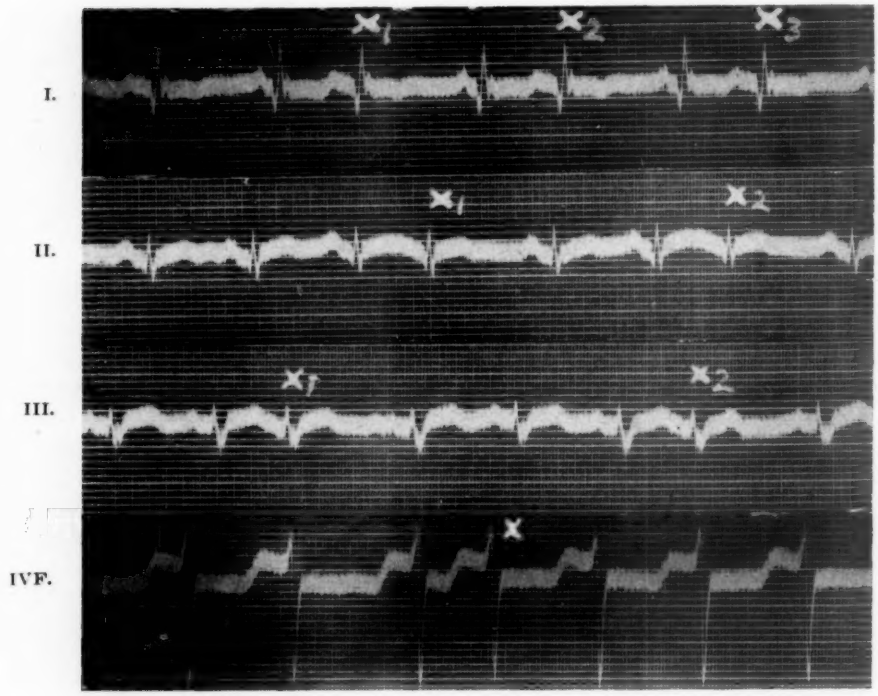


Fig. 13.—Case 2. Marked increase in aberration of APS after quinidine administration in a case of fatal atypical myocardial infarction. Record taken Dec. 21, 1941, reveals numerous APS (x_1, x_2, and x_3), with no aberration of QRS and minimal aberration of the T waves.

Case 3.—A. H., admission No. 63394, a 73-year-old man, was admitted to the Cardiac Clinic suffering from essential hypertension (blood pressure 180/100). He had no complaints referable to the heart, but presented a cardiac irregularity which, as the electrocardiogram (Fig. 15) showed, was caused by numerous APS. These APS exhibited varying degrees of aberration which did not depend on the degree of prematurity. A few beats, e. g., x_2 in the third lead, showed aberration affecting amplitude, configuration, and direction of the QRS complexes, and also an increase in the size of the T wave; other APS, on the other hand, especially those occurring a little later in diastole (x_1 in the second lead), showed only minimal aberration of QRS-T. The tracings were otherwise within normal limits for a patient of that age, with one possible exception: the low amplitude of the R wave in Lead CF_2.

The patient was then given 0.3 Gm. of quinidine sulfate three times a day, by mouth, for one week, during which time his condition did not change in any way. Another electrocardiogram was taken at the end of that week (Fig. 16). The normal beats of the second record showed only slight changes from those of the first (lower amplitude of the T waves in all leads, and prolongation of the Q-T interval from the original 0.37 second to 0.42 second, measured in Lead CF_2). The APS of the second record, however, were for the most part markedly different. A few still showed little aberration, e. g., x_3 in Lead II,

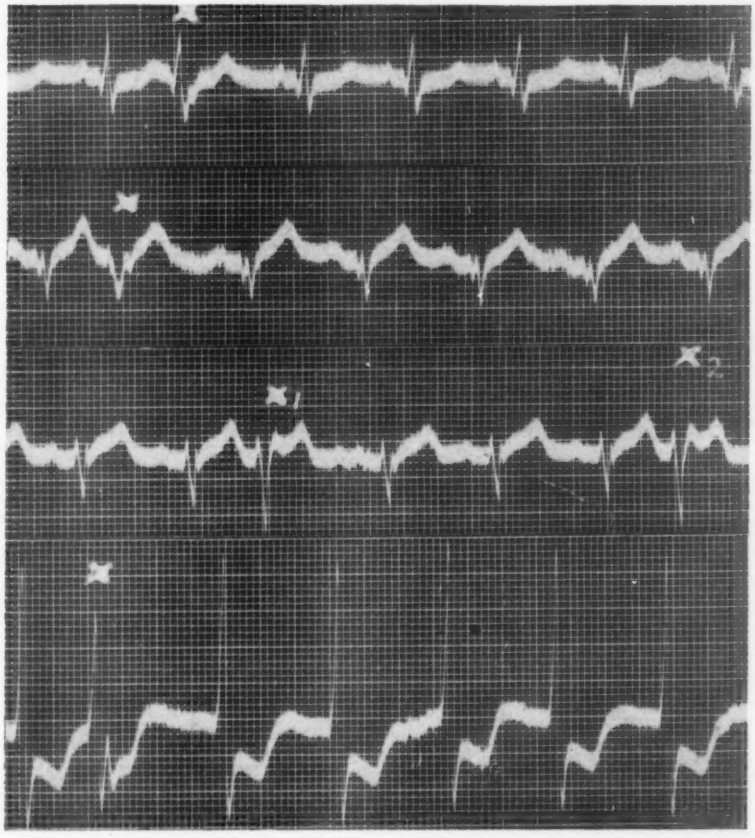
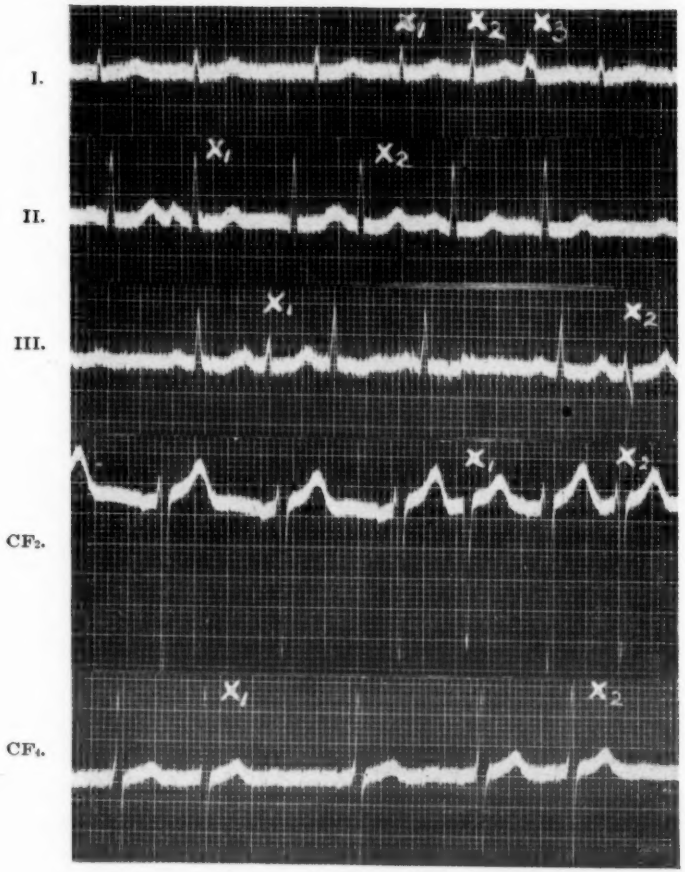


Fig. 14.—Case 2. Marked increase in aberration of APS after quinidine administration in a case of fatal atypical myocardial infarction. Record taken Dec. 23, 1941, shows APS (x, x_1, and x_2) with fairly marked aberration [increase in amplitude of QRS (Lead III), change in duration of QRS (Lead II), change in configuration of QRS (Lead IVF), elevation of RS-T junction (Lead III), increase in amplitude of the T waves (Lead I)].

In the interval between these two records, the patient had received 1.8 Gm. of quinidine sulfate. She died Dec. 24, 1941.

but the majority showed marked aberration. The duration of the QRS complex particularly was affected; it was increased to 0.13 second from a previous maximum of 0.10 second (x_2 in Lead I and x_1 in Lead II). (Incidentally, several APS showing much aberration were *not* more premature than others showing little aberration.) The increase in aberration which had occurred within one week was most



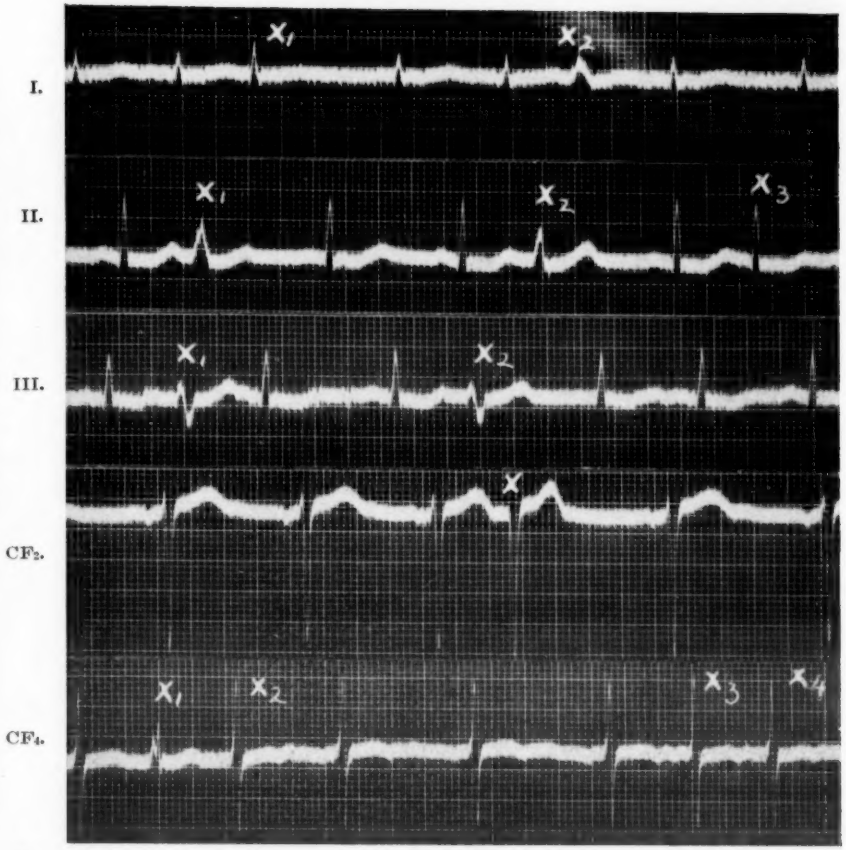


Fig. 15.—Case 3. Marked increase in aberration of APS after quinidine administration in a case of essential hypertension. Record taken March 22, 1944, reveals numerous APS (x_1, x_2, and x_3) with varying degrees of aberration.

Fig. 16.—Case 3. Marked increase in aberration of APS after quinidine administration in a case of essential hypertension. Record taken March 29, 1944, again shows numerous APS (x_1, x_2, and x_3). There is now a marked increase in aberration. x_2 in Lead I shows marked increase in duration of QRS as compared to x_3 in Lead I of Fig. 15. x_1 and x_2 in Lead II show increase in duration and change in configuration of QRS as compared to x_1 and x_2 of Lead II in Fig. 15. x_1 and x_2 in Lead III show marked increase in duration and change in configuration of QRS as compared to x_2 in Lead III of Fig. 15.

In the interval between these two records, the patient had received 6.3 Gm. of quinidine sulfate.

striking. In the absence of any clinical change, there could be little doubt that it was the result of quinidine administration.

This case, we believe, sheds a good deal of light on the problem of aberration. Quinidine is a drug known to slow intraventricular conduction. In this instance, it had little effect on the intraventricular conduction time of the normal beats, but it selectively affected the intraventricular conduction time of the APS.* The cause of this selective action is not known, but it may well lie in the prematurity of the APS. The APS occurred so early in diastole that the conducting tissues had not yet fully recovered from their activity during the preceding normal beat, and their state of incomplete recovery might have made them more vulnerable to the action of quinidine.

The three cases just reported were selected from a much larger number of patients who had serial records. In many of these, multiple APS were present, and aberration varied a great deal within one lead; it would have been difficult to compare these records with subsequent ones. Such electrocardiograms were obviously unsuitable for correlation with clinical observations. Other cases had to be eliminated for a different reason. After the administration of quinidine, the electrocardiograms frequently showed no more APS at all; they had been abolished by quinidine. Our total number of suitable serial records is, therefore, too small for statistical analysis, yet we believe that the three cases reported here, together with the facts previously presented, may serve as a basis for the following conclusions.

CONCLUSIONS

Aberration of the ventricular complexes of APS reflects changes in the intraventricular conduction system. These changes may be physiologic, e.g., if the APS occur very early in diastole; or they may be pathologic. In the latter case, they may be brought about by diseases or by drugs affecting intraventricular conduction, of which quinidine is an example. More important than aberration itself is a change in the degree of aberration. Such a change is always a significant electrocardiographic findings. It indicates a change in the condition of the patient's heart which the remainder of the electrocardiogram may not clearly show. In two of our cases, the change was probably brought about by the administration of quinidine, and, in the third, by a severe infection (pneumonia). Other factors will probably come to light once the subject of aberration receives more attention. Serial records of patients with APS are especially worthy of study. If changes in the clinical condition of such patients occur, serial records should be analyzed for possible changes in the degree of aberration. For the same reason, serial records should be taken of patients with APS if they receive quinidine or other drugs known to affect the electrocardiogram.

*A pathologic condition likewise can affect the configuration of premature systoles selectively, as was recently demonstrated by Dressler[12] in a case of acute myocardial infarction masked by bundle branch block. In Dressler's case, the electrocardiographic changes indicative of infarction were absent in the normal beats, but were displayed by *ventricular* premature systoles.

SUMMARY

1. The electrocardiograms of 201 patients who had auricular premature systoles (APS) were analyzed. One thousand three hundred six APS were found, and were divided into five groups according to the degree of their prematurity. Multiple APS of the same degree of prematurity occurring in one record were counted as one "type." Multiple APS of different degrees of prematurity were counted as different "types." The total number of "types" of APS was 525. Eight of these were blocked.

2. APS with aberration of the ventricular complexes were three times as frequent as APS without aberration.

3. If no aberration is present, the APS may be overlooked, or the irregularity may be misinterpreted as sinus arrhythmia.

4. Aberration, especially of the T wave, is often more marked in the chest leads. Chest leads may thus aid in the recognition of APS.

5. Forty-three types showed no aberration of QRS, but showed aberration of the RS-T segments or the T waves.

6. Three hundred thirty-seven types of APS showed aberration of the QRS complexes.

7. If aberration of QRS was of slight degree, increase or decrease in amplitude was the most frequent single change; changes in configuration (slurring, notching, appearance of a Q wave) were next in frequency; changes in duration occurred seldom except in conjunction with other changes; a reversal of direction never occurred alone.

8. The higher degrees of aberration were less frequent than the lower. They consisted of changes in amplitude combined with changes in configuration, or various combinations of changes in amplitude, configuration, duration, and direction.

9. The highest degree of aberration (twenty-eight types) affected all four characteristics of the QRS complex, amplitude, configuration, duration, *and* direction. APS with such bizarre ventricular complexes are commonly mistaken for ventricular premature systoles.

10. The degree of prematurity of an APS is a major factor in determining the degree of its aberration. This was shown by the following facts:

a. None of the twenty-eight types of APS with very marked aberration occurred late in diastole.

b. None of the thirty-five types of APS without any aberration occurred very early in diastole.

c. None of the 101 types of APS occurring late in diastole showed more than moderate aberration.

d. None of the six types of APS occurring *very* early in diastole were free from aberration.

11. The degree of prematurity is not the only factor which determines the degree of aberration. This was shown by the following facts:

a. Of one hundred types of APS occurring early in diastole, eleven showed no aberration.

b. Most electrocardiograms showing different types of APS in the same record revealed a lack of parallelism between aberration and the degree of prematurity; aberration often remained the same or became less marked as the degree of prematurity increased.

12. No definite relationship was found to exist between the number of APS in a given record and the aberration of their ventricular complexes.

13. P-R interval changes in APS had no influence on the aberration of their ventricular complexes.

14. The patient's age had no influence on aberration. APS with marked aberration were found in children. APS without any aberration were found in patients over 70 years of age.

15. Aberration occurred in normal and abnormal electrocardiograms. Aberration of all degrees occurred in noncardiac patients as frequently as in cardiac patients. Aberration was no more frequent in the presence of congestive heart failure than in its absence.

16. Three cases are reported. Their serial records showed that significant changes in the degree of aberration of the APS occurred within a few days. In two cases, the change was probably brought about by the administration of quinidine, and, in the third, by a severe infection (pneumonia).

17. Aberration of the ventricular complexes of APS reflects changes in intraventricular conduction; these changes may be physiologic; or they may be pathologic and may then be produced by diseases or by drugs affecting the conduction system, e. g., quinidine.

18. Quinidine selectively affects APS by increasing their aberration, especially the duration of QRS.

19. A change in the degree of aberration is more significant than aberration itself. It indicates a change in the condition of the heart which the remainder of the electrocardiogram may not clearly reveal.

REFERENCES

1. Lewis, Sir Thomas: The Mechanism and Graphic Registration of the Heart Beat, Ed. 3, London, 1925, Shaw & Sons Ltd., p. 229.
2. Lewis, Sir Thomas: Clinical Electrocardiography, Ed. 4, London, 1928, Shaw & Sons Ltd., p. 65.
3. White, Paul D.: Heart Disease, New York, 1931, Macmillan Co., pp. 238 and 625.
4. White, Paul D., and Stevens, H. W.: Ventricular Response to Auricular Premature Beats and to Auricular Flutter, Arch. Int. Med. **18**: 712, 1916.
5. Carter, J. Bailey: The Fundamentals of Electrocardiographic Interpretation, J. A. M. A. **99**: 1345, 1932.

6. Pardee, Harold E. B.: Clinical Aspects of the Electracardiogram, Ed. 4, New York, 1941, Paul B. Hoeber Inc., p. 187.
7. Wenckebach, Karel Frederik, and Winterberg, Heinrich: Die unregelmässige Herztätigkeit, Leipzig, 1927, W. Engelmann, p. 191.
8. Katz, Louis, N.: Electrocardiography, Philadelphia, 1941, Lea & Febiger, p. 365.
9. Scherf, David, and Boyd, Linn J.: Clinical Electrocardiography, St. Louis, 1941, The C. V. Mosby Co., p. 189.
10. Bellet, Samuel, and McMillan, Thomas M.: Electrocardiography, in "Diagnosis and Treatment of Cardiovascular Disease" (edited by Wm. D. Stroud), Philadelphia, 1941, F. A. Davis Co., p. 636.
11. Stenstroem, Nils: An Experimental and Clinical Study of incomplete Bundle Branch Block, Acta med. Scandinav. **60:** 552, 1924.
12. Dressler, Wm.: A Case of Myocardial Infarction Masked by Bundle Branch Block but Revealed by Occasional Premature Ventricular Beats. Am. J. M. Sc. **206:** 361, 1943.

WOLFF-PARKINSON-WHITE SYNDROME WITH UNUSUAL FEATURES

CAPTAIN M. H. STEIN, M.C., ARMY OF THE UNITED STATES

THE electrocardiographic pattern of a short P-R interval associated with a QRS complex of the bundle branch block type has been described many times. In 1915, Wilson[1] described a case in which he believed that vagal stimulation produced an electrocardiogram with a short P-R and bundle branch block type of QRS, and that this was due to A-V nodal rhythm. In 1937, Bishop[2] reviewed the literature and found that forty-five cases had been reported. The first complete report of this condition was made in 1930 by Wolff, Parkinson, and White.[3]

This condition may be more frequent than is evident from the literature, inasmuch as not all cases are being reported. Wolferth and Wood[4] state that, in about a thousand electrocardiograms, one case may be encountered in which an abnormally short P-R interval is associated with a widened QRS complex, and that the latter is markedly aberrant in its initial portion. In a series of 933 patients who had electrocardiograms at this station hospital in the past year, this electrocardiographic pattern was found three times.

All authors agree that this syndrome, per se, is not indicative of organic heart disease. In the series of eleven cases reported by Wolff, Parkinson, and White[3] there were only two cases in which there was evidence of organic heart disease. In Wolferth and Wood's[4] series of nine cases, there were also two patients with organic heart disease. The majority of these patients give a history of attacks of paroxysmal tachycardia of many years' duration.

In the three cases encountered at this hospital there was no evidence of organic heart disease in two, whereas, in the third, which is described in detail below, there was evidence of active rheumatic fever and rheumatic heart disease. Furthermore, this patient with rheumatic fever was the only one who gave a history of paroxysmal tachycardia; he had had it for five years prior to admission. One of the patients had no previous history of any consequence, but the second gave a history of recurrent premature contractions for many years.

Three theories have been suggested as an explanation for the syndrome:[5]

1. It is nodal rhythm or tachycardia, with aberrant conduction in the ventricle.
2. It is regular sinus rhythm, with functional intraventricular block.
3. It is regular sinus rhythm, with a shorter aberrant pathway between the sinoauricular node and ventricular musculature.

Received for publication July 3, 1944.

The third theory, also referred to as the bundle of Kent theory, has been most widely accepted. The experimental work of Butterworth and Poindexter[6] offers some evidence in favor of this theory.

The purpose of this report is not to add another case of Wolff-Parkinson-White syndrome to the literature, but to present some unusual features of this syndrome in the case to be described.

REPORT OF CASE

A 31-year-old soldier was admitted to the Station Hospital at Camp Hale, Colorado, Dec. 14, 1943, for rheumatic fever with cardiac involvement. In addition, he gave a history very suggestive of attacks of paroxysmal tachycardia during the preceding five years, one of which he had the day before admission.

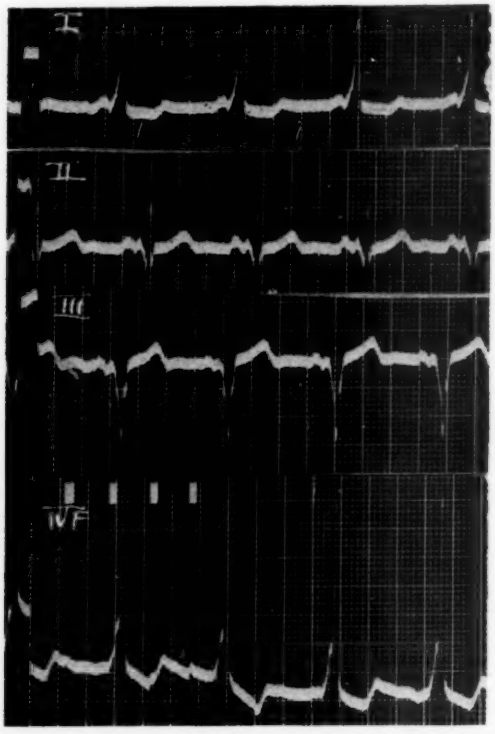


Fig. 1.—Dec. 14, 1943; Wolff-Parkinson-White syndrome.

The electrocardiogram on the day of admission showed the characteristic pattern of the Wolff-Parkinson-White syndrome, i.e., a short P-R interval with a prolonged, aberrant QRS complex of the bundle branch block type (Fig. 1).

During the latter part of his convalescence in the hospital, on April 15, 1944, the patient suddenly had an attack of cardiac palpitation; this was the same complaint which he has had for five years, and, on examination, his cardiac rate was found to be 190 per minute. The electrocardiogram at this time showed paroxysmal nodal tachycardia,

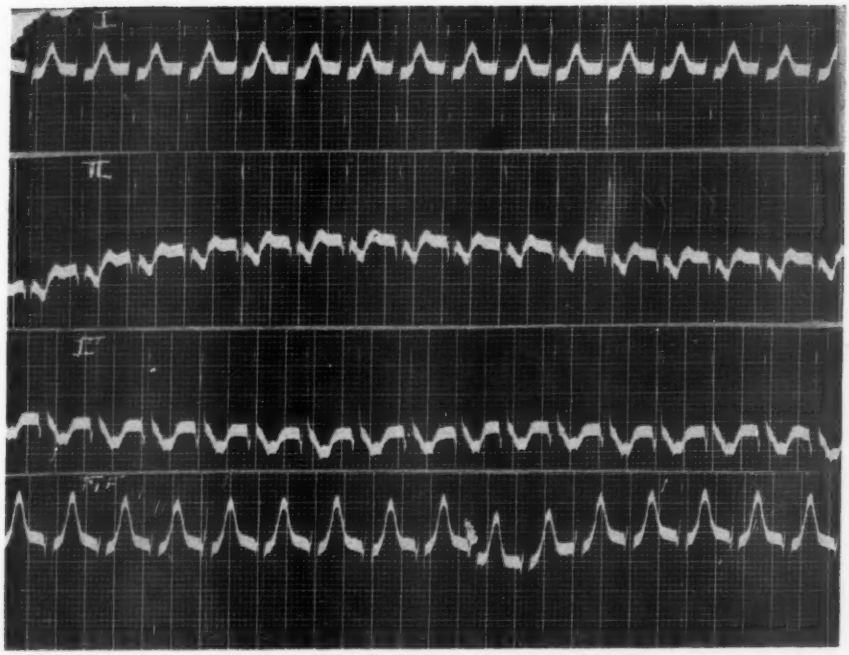


Fig. 2.—April 15, 1944; Paroxysmal A-V nodal tachycardia with disappearance of the complexes of the Wolff-Parkinson-White syndrome.

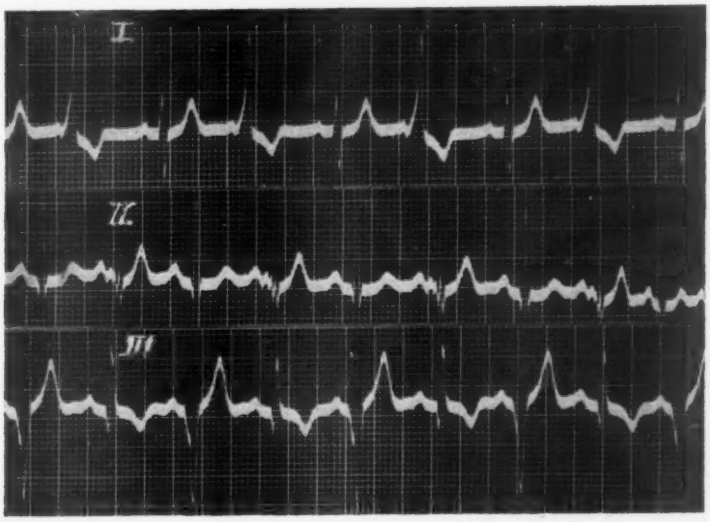


Fig. 3.—April 15, 1944; Normal P-R intervals and QRS complexes alternating with those of Wolff-Parkinson-White syndrome immediately after cessation of attack of paroxysmal nodal tachycardia.

with a rate of 170 per minute (Fig. 2). The aberrant QRS complexes were replaced by normal ones, as is characteristic of the Wolff-Parkinson-White syndrome during paroxysmal tachycardia.

This tachycardia was stopped by the Valsalva experiment, after the various other methods, usually employed, had failed. Another tracing, taken immediately after the cessation of the attack, showed an unusual feature of the Wolff-Parkinson-White syndrome, i.e., alternation of normal P-R intervals and normal QRS complexes with short P-R intervals and widened, aberrant QRS complexes (Fig. 3). Earlier during his stay in the hospital the patient had developed sinus tachycardia with a rate of 120 per minute and with a return of normal P-R intervals and normal QRS complexes; this was proved electrocardiographically. After the conclusion of this attack, also, a tracing showed the same alternation of normal and aberrant complexes as in Fig. 3.

Subsequent electrocardiograms, taken April 22, 1944, one week after the tracings shown in Figs. 2 and 3, again showed the characteristic Wolff-Parkinson-White syndrome, as Fig. 1.

COMMENT

The interesting electrocardiographic anomaly of a prolonged QRS complex with a short P-R interval, which usually occurs in healthy young persons, was encountered in this case of rheumatic fever. However, since this patient gave the usual history of paroxysmal tachycardia, in this case, for five years, one is inclined to regard the rheumatic fever and the electrocardiographic anomaly as coincidental.

The interesting feature in this case was the alternation of regular and aberrant beats after an attack of sinus tachycardia and also after an attack of paroxysmal nodal tachycardia.

Such alternation is no doubt an unusual occurrence in this syndrome, and perhaps lends weight to the theory that a shorter pathway, the bundle of Kent, does exist, and that the impulses travelled alternately along the bundle of Kent and the bundle of His to produce such an electrocardiographic picture.

CONCLUSIONS

1. In a series of 933 patients who had electrocardiograms, the Wolff-Parkinson-White syndrome was found three times.

2. The patient described in this report was admitted to the hospital because of acute rheumatic fever, but, in addition, had a history of recurrent paroxysmal tachycardia for the preceding five years.

3. The rheumatic fever and the short P-R, prolonged QRS syndrome were probably only coincidental.

4. The unusual phenomenon of normal P-R intervals and normal QRS complexes alternating with the short P-R intervals and aberrant QRS complexes of the so-called Wolff-Parkinson-White syndrome was observed in this case.

The author wishes to express his appreciation and thanks to Captain R. L. Smith for valuable guidance and help in this study.

REFERENCES

1. Wilson, F. N.: A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, Arch. Int. Med. **16**: 1008, 1915.
2. Bishop, L. F.: Bundle Branch Block With Short P-R Interval in Individuals Without Organic Heart Disease, Am. J. M. Sc. **194**: 794, 1937.
3. Wolff, L., Parkinson, J., and White, P. D.: Bundle Branch Block With Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia, AM. HEART J. **5**: 685, 1930.
4. Wolferth, C. C., and Wood, F. C.: The Mechanism of Production of Short P-R Intervals and Prolonged QRS Complexes in Patients With Presumably Undamaged Hearts, AM. HEART J. **8**: 297, 1933.
5. Fox, T. T., Travell, J., and Molofsky, L.: Action of Digitalis on Conduction in the Syndrome of Short P-R Interval and Prolonged QRS Complex, Arch. Int. Med. **71**: 206, 1943.
6. Butterworth, J. S., and Poindexter, C. A.: Short P-R Interval Associated With a Prolonged QRS Complex, Arch. Int. Med. **69**: 437, 1942.

COMPARISON OF THE THERAPEUTIC EFFECTIVENESS OF SERUM AND SODIUM CHLORIDE IN SCALD SHOCK

OSCAR HECHTER, PH.D., H. C. BERGMAN, PH.D., AND
MYRON PRINZMETAL, M.D.
LOS ANGELES, CALIF.

AS A result of the present war, burns and shock following burns have assumed increasing importance because of their high frequency among members of our Armed Forces and also among the civilian population. As yet, there is a marked difference of opinion regarding the treatment of these conditions. It is the purpose of the group of experiments presented here to ascertain more effective methods for the treatment of shock.

One of the chief aspects of the treatment of burn shock, as well as other types of traumatic shock, is the administration of fluid to help restore the lowered blood volume to normal. The solutions which have been used to replace vascular fluid loss are numerous, and include normal saline, glucose or glucose-saline solutions, saline solutions containing colloids such as serum albumin, gum acacia, or gelatin, blood serum or plasma, and whole blood. Because the vascular fluid lost in burns is essentially plasma, treatment with plasma or serum has appeared to be most logical, and is accordingly regarded as the most acceptable form of fluid therapy in burn shock.[1] Although isotonic sodium chloride solutions have been used in burn shock with good results by many, including Davidson,[2, 3] it is felt that such a colloid-free solution is only temporarily effective in shock, presumably because the colloid osmotic pressure of the animal's serum proteins is diminished by the saline infusion, with subsequent leakage of the administered fluid from the blood stream. To remove this deficiency, various colloids have been dissolved in saline solution, among which may be mentioned gum acacia, gelatin, and, more recently, bovine and human serum albumin.

Recent work, however, suggests that the concept which emphasizes the colloidal osmotic pressure of serum proteins may be inadequate to explain the therapeutic activity of plasma or serum in certain types of shock. Thus, Mylon, Winternitz, and de Süto Nagy[4] have presented evidence that there is a labile factor in plasma which, independent of colloid osmotic action, reduces mortality in tourniquet shock in dogs. We have found in animals,[5] as was independently observed by Rosenthal,[6] that sodium chloride has antiburn shock activity, thus confirming

From the Straus Research Laboratory, Cedars of Lebanon Hospital, and the University of Southern California Medical School.

Aided by grants from the Blanche May Selden Fund, the Martha Kirschner Haft Memorial Fund, F. Brice, Morton May, Walter Kirschner, and Mr. and Mrs. S. Marx.
Received for publication July 3, 1944.

earlier clinical observations. In further studies, Rosenthal showed that, in mice, the therapeutic activity of sodium chloride in burn shock is dependent upon the sodium ion,[7] and that the therapeutic action of serum in tourniquet,[8] as well as burn, shock[7] can be explained in terms of the sodium content of the serum.

Therefore, it would appear that serum and plasma may be therapeutically active in shock because the administered fluid contains: (a) sodium, (b) proteins which possess colloid osmotic activity, or (c) the labile factor of Mylon and his co-workers. Having developed a standardized method for evaluating therapeutic agents in burn shock, we have studied the relative importance of the above factors with respect to the therapeutic activity of serum in shock.

In addition, evidence has been obtained on the following questions of practical importance. (a) Is water by mouth harmful, as claimed by some?[7] (b) Is sodium chloride more effective in burn shock when administered orally or intraperitoneally than by the intravenous route?[7]

METHOD

The details of the method used in these studies have been described in a previous report,[9] and may be summarized as follows. The time-mortality curves of groups of rats or mice treated with the agents under investigation are compared with those of suitable control groups after both groups have been subjected to thermal injury under identical conditions. Standardized thermal injury is administered by immersing the entire body, except the head and neck, of etherized animals into scalding water for definite periods of time. Anesthesia was complete, and the animals had no pain. The experiments are terminated forty-eight hours after the infliction of thermal injury, and the average survival time and the percentage of survivors are ascertained. It has been found, using groups containing as many as twenty to thirty animals, wherein variable factors, such as the degree of thermal injury, body weight, sex, strain, pre-experimental nutritional regime, and hydration, are adequately controlled, that variations in either the average survival time or in percentage mortality occur between untreated groups which are statistically significant. This means that a variable is operative in the method which may give rise to erroneous evaluation of antiburn shock activity. It is, therefore, apparent that an inactive substance, in a single test, using as many as thirty animals to a group, may appear to have therapeutic activity. Contrariwise, it is possible to obtain apparently negative results with a therapeutically active agent. However, it has been shown that, by doing a large number of experiments, this difficulty is overcome if therapeutic activity be evaluated by the consistency with which responses are obtained. Thus, an active therapeutic agent, on repeated testing, using groups of twenty to thirty animals, although it shows an occasional negative result, will, in the majority of tests, elicit positive responses; and conversely, inactive substances will show negative results in most tests, although occasional positive responses may be obtained.

In these experiments, the usual method of producing burn shock was to immerse anesthetized mice, weighing approximately 20 grams, for ten seconds in water at 65° C., whereas etherized rats, weighing from

150 to 200 grams, were scalded at 70° C. for ten seconds. The agents under investigation were administered approximately one hour after scalding (unless otherwise stated) to animals which were not at that time moribund, and a similar group, which received control solutions or no treatment, served as a control.

A. Influence of Route of Administration on Activity of Sodium Chloride.—In evaluating the influence of the route of administration on the therapeutic activity of sodium chloride, Rosenthal[7] concluded that intravenous administration was less effective than oral or intraperitoneal administration. In view of the importance of ascertaining whether the intravenous route is, in reality, less effective than the oral or intraperitoneal, the effectiveness of administering sodium chloride by these various routes has been evaluated by repeated testing.

In these experiments, mice were divided into five groups one hour after scalding; one group served as a control, and the other groups received 1 c.c. of 0.9 per cent sodium chloride solution either intravenously, intramuscularly, intraperitoneally, or orally. Table I gives the results obtained in four trials on 481 mice and in one experiment with forty-four rats. It will be seen that saline, independent of the route of administration, increased the average survival time and decreased the mortality. The average survival time was increased 84, 95, 100, and 69 per cent by giving isotonic salt solution by the intravenous, intraperitoneal, oral, and intramuscular routes, respectively, in the four experiments in which mice were employed. Although it might appear that the results with the intravenous and intramuscular routes were somewhat less satisfactory than with oral or intraperitoneal administration, these differences are not significant in view of the wide variation in the method. In individual trials, it will be seen that saline intravenously may be better, the same as, or worse than saline administered by mouth or intraperitoneally. The survival time was increased over the untreated controls by 28, 26, 31, and 17 per cent by administering saline by the intravenous, intraperitoneal, oral, and intramuscular routes, respectively. Again, these values are not significantly different. It is apparent that had only one experiment been performed, erroneous conclusions may have been derived, although it is possible by chance that correct evaluation may have been obtained. It would therefore seem that the route of administration has little effect upon the antiburn shock activity of sodium chloride.

B. Comparison of the Therapeutic Activity of Sodium Succinate and Sodium Chloride.—The fact that sodium chloride has therapeutic activity in this type of burn shock raises the question as to which ion is the important agent. In testing this point, an isotonic solution of sodium succinate was compared to isotonic sodium chloride; both solutions were given by mouth, one hour after scalding. Attention was given the possibility that the succinate possessed specific therapeutic activity in shock,

TABLE I

ADMINISTRATION OF ISOTONIC SALINE BY DIFFERENT ROUTES

ANIMAL	NO TREATMENT			INTRAVENOUS			INTRAPERITONEAL			ORAL			INTRAMUSCULAR		
	NUMBER OF ANIMALS	AVERAGE SURVIVAL TIME (HR.)	SURVIVORS (%)	NUMBER OF ANIMALS	INCREASE IN SURVIVAL TIME (%)	INCREASE IN SURVIVORS (%)	NUMBER OF ANIMALS	INCREASE IN SURVIVAL TIME (%)	INCREASE IN SURVIVORS (%)	NUMBER OF ANIMALS	INCREASE IN SURVIVAL TIME (%)	INCREASE IN SURVIVORS (%)	NUMBER OF ANIMALS	INCREASE IN SURVIVAL TIME (%)	INCREASE IN SURVIVORS (%)
Mice	25	19.9	32	24	97	43	25	81	28	25	83	32	25	39	4
	23	20.4	30	23	43	18	23	62	22	23	86	35	23	56	14
	22	7.7	0	22	136	9	22	173	14	21	168	19	21	130	14
	28	26.0	36	27	61	42	27	63	38	27	61	38	28	53	36
Rats	11	6.9	0	11	195	36	11	485	82	11	224	27			

in view of the report by Mylon, et al.,[4] that succinate treatment increased the survival time of dogs subjected to tourniquet shock.

Table II, *A* shows the results obtained on 331 mice in five trials. It will be seen that, on the average, sodium chloride increased the survival time 144 per cent, whereas sodium succinate increased it 146 per cent. The survival was increased 28 and 27 per cent by sodium chloride and sodium succinate, respectively. These data demonstrate that sodium succinate is as effective as, but is not superior to, sodium chloride. This confirms Rosenthal's contention concerning the importance of the sodium ion. Further, these data show that the succinate ion, in the dosages employed, is without benefit in scald shock.

C. Comparison of Isotonic Glucose With Sodium Chloride.—The question arises whether isotonic salt solution is useful in this type of shock by virtue of its sodium content, or because it is isotonic. To answer this question, the effectiveness of isotonic sodium chloride was compared to that of isotonic glucose, given intravenously.

Table II, *B* illustrates the results obtained on 478 animals in seven trials. It will be seen that glucose, on the average, increased the survival time 82 per cent, and the percentage of survivors, 8 per cent. Saline is more effective than glucose because the survival time was increased 124 per cent, and the percentage of survivors was increased 24 per cent. Saline was definitely active in five of the seven trials, whereas glucose was superior to the control in only three of seven instances. In comparing glucose and saline, it was observed that glucose was definitely inferior in five of the seven trials. These data, therefore, demonstrate that, although glucose is somewhat effective, an equivalent volume of

TABLE II

INFLUENCE OF VARIOUS SOLUTIONS ON SCALD SHOCK

PROCEDURE	NUMBER OF TRIALS	TOTAL NUMBER OF MICE	MEAN OF AVERAGE SURVIVAL TIME (HR.)	MEAN OF PERCENTAGE OF SURVIVORS	MEAN OF PERCENTAGE INCREASE IN AVERAGE SURVIVAL TIME OVER CONTROLS	MEAN OF INCREASE IN PERCENTAGE OF SURVIVORS OVER CONTROLS
A						
No treatment		113	14.7	13		
Saline	5	109	35.9	41	144	28
Sodium succinate		109	36.1	40	146	27
B						
No treatment		164	15.2	15		
Saline	7	154	34.0	41	124	26
Glucose		160	27.5	23	81	8
C						
No treatment		174	15.9	18		
Saline	7	158	27.8	41	75	23
Water		163	21.8	32	37	14
D						
No treatment		113	14.7	13		
Glucose	5	99	31.6	26	115	13
Glucose-gelatin		95	20.9	13	42	0

sodium chloride has a therapeutic action over and above that of fluid replacement, as represented by glucose administration. The results with glucose do not permit conclusions to be drawn as to whether the glucose or the fluid is responsible for the decreased mortality observed.

D. Effect of Water by Mouth.—In view of the fact that many patients in shock are thirsty, it is important to know the effect of the oral administration of water. Does water help in shock, or is it actually deleterious, as has been reported?[7] To obtain information on this point, the effect of giving water by mouth was compared with that of orally administered isotonic salt solution.

Table II, *C* shows the results obtained on 495 animals in seven trials. It is evident from repeated testing that, although water is less effective than saline, it is, nevertheless, not toxic. On the contrary, water may slightly decrease mortality, although the data are not sufficient to draw a final conclusion regarding this point.

E. Comparison of Homologous Serum With Sodium Chloride.—It has generally been held that serum or plasma is therapeutically superior to saline intravenously in burn shock. This view, however, is not supported by Rosenthal,[7] who, in a single trial, showed that saline was as effective as homologous serum in decreasing mortality among mice after scalding. It was important to ascertain whether or not saline is actually as effective as serum in this type of burn shock.

In these experiments, rats were the test animals. Rat serum was compared to an equivalent volume of saline, and both solutions were given via the tail vein after scalding. Table III shows the results obtained on 216 animals. It will be seen that, under the conditions of these experiments, saline was as effective as serum, and it thus appears that the therapeutic activity of serum can be ascribed to its sodium content.

F. Comparison of Gelatin-Glucose With Isotonic Glucose Solution.—The fact that saline was as effective as serum in reducing mortality

TABLE III

RELATION OF INTRAVENOUS ADMINISTRATION OF SALINE AND SERUM TO SCALD SHOCK

PROCEDURE	FLUID INJECTED AS PERCENTAGE OF BODY WEIGHT	TIME OF INJECTION AFTER SCALDING (HR.)	NUMBER OF RATS	AVERAGE SURVIVAL TIME (HR.)	SURVIVORS (%)	INCREASE IN AVERAGE SURVIVAL TIME OVER CONTROLS (%)	INCREASE IN PERCENTAGE OF SURVIVORS OVER CONTROLS
No treatment			21	10.6	5		
Saline	4%	1.0	29	24.8	28	134	23
Serum			28	22.8	21	115	16
No treatment	2%	1.5	13	12.7	15		
Saline	(adminis-	and	46	27.4	39	116	24
Serum	tered twice)	4.5	41	31.2	34	146	19
Saline			19	27.2	32		
Serum	2%	1.5	19	25.3	16		

strongly suggests that the colloid osmotic activity of protein in this form of burn shock has little influence on survival. To check this conclusion, the effect of gelatin was ascertained, for gelatin possesses colloid osmotic activity and is useful as a plasma substitute.[10, 11]

The gelatin solution used in these experiments was prepared by autoclaving a 5 per cent solution of gelatin (Wilson), dissolved in isotonic glucose solution (5.5 per cent) for fifteen minutes at 25 pounds' pressure. The effectiveness of this gelatin-glucose solution in decreasing mortality was compared to that of a solution of glucose, employing mice as the test animals. The solutions were injected intravenously, approximately one hour after thermal injury.

The results obtained on 307 mice are shown in Table II, *D*; they demonstrate that the addition of gelatin to isotonic glucose solution does not increase the therapeutic activity, as should be the case if the colloid osmotic activity of protein were important in this type of burn.

DISCUSSION

Using the scalding method for the production of burn shock, it has been found on repeated testing that isotonic sodium chloride solution is equally effective when administered intravenously, intraperitoneally, intramuscularly, or orally. This contradicts the contention that saline intravenously is less effective than equivalent volumes administered by the oral or intraperitoneal route.[7]

In comparing the therapeutic activity of sodium chloride with sodium succinate, equivalent results were obtained, as has been previously reported by Rosenthal, thus confirming the view that the sodium, and not the chloride, ion is responsible for the therapeutic response obtained with saline.[7] In view of the report that succinate is therapeutically useful in tourniquet shock,[4] the demonstration that sodium succinate was not superior to sodium chloride serves to indicate that succinate, in the doses employed, was without specific therapeutic value in this type of shock.

The fact that isotonic glucose solution, although it is effective in decreasing mortality, is less active than an equivalent volume of sodium chloride demonstrates that the activity of the sodium is not merely one of simple replacement of isotonic fluid, and suggests that the sodium has a specific action in combating this type of burn shock. The fact that glucose is helpful may be due in part to simple fluid replacement or to a possible specific effect of glucose.

It has been found that the oral administration of water is not toxic, as some believe,[7] but may possibly be of some benefit.

Finally, it has been shown in this type of burn shock that the intravenous administration of protein, which has colloid osmotic activity, does not influence survival after thermal injury, for it has been shown

that saline is as effective as serum and that the addition of 5 per cent gelatin to isotonic glucose solution does not enhance the therapeutic effect. It may be pointed out that if there is a labile factor in plasma which exerts some specific therapeutic action in shock, as Mylon, Winternitz, and de Süto Nagy[4] have suggested, these experiments demonstrate no such activity in serum in scald shock.

In considering the significance of these results for clinical burn shock, it should be emphasized that the method employed in these studies subjects a relatively large surface of the body to relatively low temperatures, varying from 65° to 75° C. On the other hand, burns by very high temperatures, involving a relatively small surface of the body, also produce shock. In the latter instance, injury to tissues beneath the skin occurs, whereas, with low temperature burns, the damage produced in our experiments was restricted to superficial tissues. It does not necessarily follow that, because shock develops in both instances after thermal injury, the mechanism of shock production is similar. Elman[12] has also suggested this difference.

With this point of view, the results of this study may prove to be applicable to the clinical shock which follows superficial burns involving large areas of the body. In this type of burn, it would appear that saline treatment should be effective by all routes of administration. There would appear to be no necessity to administer isotonic sodium salt solution in clinical burn shock by the oral route exclusively, as has been so successfully done by Fox,[13] for the view that intravenous treatment is ineffective has been shown in this study not to be tenable. Although the oral route admittedly has marked advantages over other routes of administration in those instances in which, for one reason or another, salt solution cannot be given by mouth (i.e., patients with burns involving the mouth, throat, etc., or patients with persistent vomiting), the intravenous route, combined with hypodermoclysis, may possibly be used advantageously. In most instances, however, the treatment advocated by Fox would appear to be most efficacious for practical purposes.

There would appear to be no contraindication to the administration of water because of a postulated toxic action, for it has been shown that water is without toxic effect, and may, in fact, be of slight value. Water, however, is much inferior to the oral administration of isotonic salt solution.

It must be emphasized that the above conclusions are applicable to the shock resulting from this type of experimental thermal injury. Although Rosenthal[8] has shown that a similar situation may exist in tourniquet shock, it would appear premature to apply these suggestions to all types of shock. It is possible that shock due to burns may be of several types, and each type may require a different kind of therapy. At the present time, we are investigating this point.

CONCLUSIONS

1. Sodium chloride has therapeutic activity in burn shock, and the therapeutic agent appears to be the sodium ion.

2. Sodium chloride appears to be equally effective when administered by the intravenous, oral, intraperitoneal, or intramuscular routes.

3. The therapeutic activity of sodium chloride cannot be explained as due to simple fluid replacement, for equivalent volumes of isotonic glucose are less effective.

4. The oral administration of water is not deleterious, and may actually be of slight benefit.

5. The therapeutic activity of serum appears to be due to its content of sodium, for it has been shown that (a) serum is no more effective than equivalent volumes of saline, and (b) the colloid osmotic activity of gelatin solutions has no influence on mortality.

6. There does not seem to be a specific antishock factor in serum.

7. These conclusions hold for the specific type of shock in rats and mice which follows scalding, and cannot as yet be applied to other forms of shock.

REFERENCES

1. Harkins, H. N.: The Treatment of Burns, Springfield, 1942, Charles C Thomas.
2. Davidson, E. C.: Sodium Chloride Metabolism in Cutaneous Burns and Its Possible Significance for a Rational Therapy, Arch. Surg. 13: 262, 1926.
3. Davidson, E. C.: Tannic Acid in Treatment of Burns, Surg., Gynec. & Obst. 41: 202, 1925.
4. Mylon, E., Winternitz, M. C., and de Süto Nagy, G. J.: Studies on Therapy in Traumatic Shock, Am. J. Physiol. 139: 313, 1943.
5. Prinzmetal, M., Hechter, O., Margoles, C., and Feigen, G.: A Principle From Liver Effective Against Shock Due to Burns, J. A. M. A. 122: 720, 1943.
6. Rosenthal, S. M.: Experimental Chemotherapy of Burns and Shock. I. Methods. II. Effects of Local Therapy Upon Mortality From Shock, Pub. Health Rep. 57: 1923, 1942.
7. Rosenthal, S. M.: Experimental Chemotherapy of Burns and Shock. III. Effects of Systemic Therapy on Early Mortality, Pub. Health Rep. 58: 513, 1943.
8. Rosenthal, S. M.: Experimental Chemotherapy of Burns and Shock. IV. Production of Traumatic Shock in Mice. V. Therapy With Serum and Sodium Salts, Pub. Health Rep. 58: 1429, 1943.
9. Prinzmetal, M., Hechter, O., Margoles, C., and Feigen, G.: A Principle From Liver Effective Against Shock Due to Burns, J. Clin. Investigation 23: 795, 1944.
10. Ivy, A. C., Greengard, H., Stein, I. F., Jr., Grodius, F. S., and Dutton, D. F.: Effect of Various Blood Substitutes in Resuscitation After Otherwise Fatal Hemorrhage, Surg., Gynec. & Obst. 76: 85, 1943.
11. Parkins, W. M., Koop, C. E., Riegel, C., Vars, H. M., and Lockwood, J. S.: Gelatin as Plasma Substitute With Particular Reference to Experimental Hemorrhage and Burn Shock, Ann. Surg. 118: 193, 1943.
12. Elman, R.: Personal communication.
13. Fox, C. L., Jr.: Oral Sodium Lactate in the Treatment of Burn Shock, J. A. M. A. 124: 207, 1944.

THE ROLE OF THE RENAL PRESSOR SYSTEM IN BURN SHOCK

OSCAR HECHTER, PH.D., H. C. BERGMAN, PH.D., AND
MYRON PRINZMETAL, M.D.
LOS ANGELES, CALIF.

IT HAS been recently shown that, in certain hypotensive states, renin is released from the kidneys.[1-3] This may represent a homeostatic mechanism for maintaining arterial pressure, and would appear to be important in the hypotension which often accompanies shock. In fact, Bahnson[4] found that nephrectomized rats had a greater fall in arterial pressure and died after the removal of smaller amounts of blood than did sham-nephrectomized controls. A priori, one might not expect that the renal pressor system would be of great importance because of tachyphylaxis due to the rapid exhaustion of hypertensinogen. Having developed a method for producing standardized shock,[5] we undertook experiments to ascertain whether or not the renal pressor system has any effect on survival time and mortality of rats subjected to a scalding burn.

Experiment 1. Effect of Nephrectomy on Resistance to Burn Shock.—If the renal pressor system is important in combating shock due to thermal injury, nephrectomized animals which are unable to secrete renin should be less resistant than animals with intact kidneys. This lowered resistance should be evidenced by an increased mortality and a decreased survival time after thermal injury.

Long-Evans rats, weighing 150 to 265 grams, were used in these and subsequent experiments. The animals were etherized, and the kidneys were removed through lumbar incisions. The control animals for this experiment were sham nephrectomized in a manner designed to reproduce the trauma and manipulation involved in the nephrectomy operation.

Three to four hours after the operation, the resistance of nephrectomized and sham-nephrectomized animals to burn shock was evaluated by the following procedure. The entire body, except the head and neck, of etherized animals was immersed in water at 70° C. for ten seconds. After the scalding, the two groups were separated, placed in cages, and observations on survival were made during the next forty-eight hours. The time mortality curves for both nephrectomized and sham-nephrectomized animals were compared in eight experiments, using a total of ninety-one nephrectomized rats and ninety control rats. The data in

From the Straus Research Laboratory, Cedars of Lebanon Hospital, and the University of Southern California Medical School.

Aided by grants from the Blanche May Selden Fund, the Martha Kirschner Haft Memorial Fund, F. Brice, Morton May, Walter Kirschner, and Mr. and Mrs. S. Marx.
Received for publication July 3, 1944.

TABLE I

EFFECT OF NEPHRECTOMY ON RESISTANCE TO BURN SHOCK

PROCEDURE	NUMBER OF RATS	AVERAGE SURVIVAL TIME (HR.)	SURVIVORS (%)	TIME OF 50% MORTALITY (HR.)	INCREASE IN AVERAGE SURVIVAL TIME OVER CONTROLS (%)	INCREASE IN SURVIVORS OVER CONTROLS (%)
Nephrectomy	15	29.7	0	21		
Sham	15	40.3	87	(48 – 13%)	–26	–87
Nephrectomy	11	23.4	0	16		
Sham	10	40.0	60	(48 – 40%)	–42	–60
Nephrectomy	15	21.0	0	16		
Sham	15	36.5	53	(48 – 47%)	–42	–53
Nephrectomy	10	19.2	0	16		
Sham	10	45.6	70	(48 – 30%)	–58	–70
Nephrectomy	10	16.5	0	16		
Sham	10	33.0	30	40	–50	–30
Nephrectomy	10	27.6	0	23		
Sham	10	43.2	70	(48 – 30%)	–36	–70
Nephrectomy	10	23.9	0	16		
Sham	10	44.8	90	(48 – 10%)	–47	–90
Nephrectomy	10	24.5	0	16		
Sham	10	34.4	50	40	–29	–50

Table I show that nephrectomized animals uniformly had a significant decrease in percentage of survival rate and a decrease in the average survival time.

The above experiments demonstrate that nephrectomized animals have decreased resistance to thermal injury. However, it would be erroneous to conclude from these data that this lowered resistance is due to the absence of the renal pressor system. It is evident that removal of the kidneys also removes their excretory function, and it is therefore possible that the differences observed could be due to the effect of renal excretory insufficiency.

Experiment 2. Comparison of Nephrectomized and Ureter-Ligated Rats.—To ascertain whether the decreased resistance of nephrectomized rats to scalding is due to removal of the renal pressor system or to excretory insufficiency, ureter-ligated rats were compared to nephrectomized animals. The experiment was designed to produce an approximately equal degree of excretory insufficiency, but the ureter-ligated animals possessed an intact, but perhaps not completely functioning, renal pressor system. Therefore, if the renal pressor system has anti-burn shock activity, the ureter-ligated animals should be able to withstand shock due to burns better than the nephrectomized animals.

To test this point, four experiments, using a total of one hundred seventeen rats, were performed. The ureter ligations were performed through bilateral lumbar incisions; the ureters were ligated near the renal pelvis. Since ureter ligation does not produce immediate excretory insufficiency, because for a short while urine is excreted into the renal pelvis, the ureter ligations were performed five to six hours prior to scalding, whereas the nephrectomized rats were burned three to four hours after the operation.

TABLE II

COMPARISON OF NEPHRECTOMIZED AND URETER-LIGATED RATS

PROCEDURE	NUMBER OF RATS	AVERAGE SURVIVAL TIME (HR.)	SURVIVORS (%)	TIME OF 50% MORTALITY (HR.)
Nephrectomy	20	37.9	45	40
Ureter-Ligated	20	32.7	0	40
Nephrectomy	15	23.0	0	22
Ureter-Ligated	15	26.0	0	14
Nephrectomy	15	17.0	0	14
Ureter-Ligated	15	16.0	0	14
Nephrectomy	12	27.1	0	19
Ureter-Ligated	5	15.0	0	16

The results obtained in this experiment are shown in Table II. It will be seen that the ureter-ligated animals did not exhibit superior resistance to scald shock, as compared with nephrectomized rats. Non-protein nitrogen estimations performed on preagonal animals revealed equally marked elevations in both groups.

These results demonstrate that the renal pressor system, which is present in ureter-ligated animals, had no effect on resistance to burn shock. Although ureter ligation is said to stimulate the renal pressor system, temporarily at least, with resultant hypertension,[6] evidence has also been presented that, in more prolonged experiments, ureter ligation may inhibit the renal pressor system.[7] This experiment would seem to demonstrate that the renal pressor system is unimportant, for animals with an intact renal pressor system and renal excretory insufficiency were not more resistant than animals with an equal degree of excretory insufficiency.

Experiment 3. The Effect of Renal Excretory Insufficiency.—In the first experiment, it was shown that nephrectomized rats are less able to withstand thermal trauma than are sham-nephrectomized rats. It was suggested that this could have been due to renal excretory insufficiency. Examination of the data revealed that the nephrectomized animals died, in the majority of instances, between sixteen and forty hours after trauma; the average was twenty-four hours. In order to ascertain whether the lowered resistance to trauma was due to renal insufficiency, the effect of this factor was studied in the following manner. It was felt that if impairment of the renal excretory function was important, animals nephrectomized twenty-four hours previously should be more

TABLE III

EFFECT OF RENAL EXCRETORY INSUFFICIENCY

SCALDING TIME AFTER NEPHRECTOMY (HR.)	NUMBER OF RATS	AVERAGE SURVIVAL TIME (HR.)	SURVIVORS (%)	TIME OF 50% MORTALITY (HR.)
4	12	40.6	33	40
24	11	19.6	0	16
4	12	27.1	0	19
24	12	13.6	0	16

TABLE IV

EFFECT OF NEPHRECTOMY IN SEVERE SHOCK

PROCEDURE	SCALDING TEMPERATURE (° C.)	CONDITIONS TIME (SEC.)	NUMBER OF RATS	AVERAGE SURVIVAL TIME (HR.)	SURVIVORS (%)	TIME OF 50% MORTALITY (HR.)	INCREASE IN AVERAGE SURVIVAL TIME OVER CONTROLS (%)	INCREASE IN SURVIVORS OVER CONTROLS (%)
Nephrectomy	90	20	21	3.3	0	3.0	0	0
Sham			21	3.3	0	3.0		
Nephrectomy	85	20	10	4.1	0	3.5	–24	0
Sham			10	5.4	0	4.0		
Nephrectomy	80	15	9	10.0	0	4.5	– 1	0
Sham			7	10.1	0	4.0		
Nephrectomy	75	15	13	12.4	0	8.0	– 7	0
Sham			11	13.3	0	8.0		
Nephrectomy	75	10	10	20.2	0	16.0	–10	–20
Sham			10	22.4	20	16.0		

sensitive to thermal trauma than animals nephrectomized only a short while prior to trauma.

The results of two experiments, using a total of forty-seven animals, are shown in Table III. It will be seen that rats which were nephrectomized twenty-four hours previously were markedly less resistant than recently nephrectomized rats. This, then, demonstrates that a period of twenty-four hours of anuria significantly decreases the ability to withstand burn shock, and explains the decreased resistance of nephrectomized animals observed in Experiment 1. In passing, it may be of interest to point out that this observation may be of clinical significance, for it might explain the low resistance of patients with severe renal insufficiency to operative procedures.

Experiment 4. Effect of Nephrectomy in Severe Shock.—To provide further evidence for the view that the decreased resistance of the nephrectomized animals in Experiment 1 was due to renal insufficiency, and not to the absence of the renal pressor system, the following experiment was performed. By increasing the degree of thermal injury, animals are made to develop shock and die rapidly. If, under these conditions, nephrectomized rats be compared with sham-nephrectomized controls, the factor of renal insufficiency becomes less important because the animals die before the renal insufficiency becomes marked. If the renal pressor mechanism is effective, sham-nephrectomized rats should be more resistant than nephrectomized rats under these circumstances.

Five experiments were performed in which nephrectomized and sham-nephrectomized animals were anesthetized and then scalded at temperatures varying from 75° C. to 90° C. from ten to twenty seconds. These conditions produce a greater degree of thermal injury than that obtained in all of the previous experiments. This is evident from the fact that the control animals died rapidly, with an average survival period varying from three to twenty-three hours, in contrast to Experiment 1, in which the average survival time varied from thirty-three to forty-five hours.

The results (Table IV) show that, under these conditions of rapid mortality, there is no significant difference between nephrectomized and sham-nephrectomized rats. Thus it is clear that, when the factor of renal insufficiency is largely eliminated, the renal pressor system of the sham-nephrectomized rats had no significant effect upon mortality and survival time.

DISCUSSION

Experiments were designed to ascertain the role of the renal pressor system in scald shock. It was first found that nephrectomized animals appeared to be less resistant to shock than control animals when the degree of thermal injury was such that the control animals died with average survival periods of thirty-three to forty-five hours. It was thought that this might be due to either the effect of renal insufficiency

or to the operation of the renal pressor system. It was next shown that, if the factor of renal insufficiency was controlled by comparing ureter-ligated animals with nephrectomized animals, the presence of the renal pressor system was ineffective, for no difference was observed. Next, it was demonstrated that a twenty-four-hour period of renal insufficiency markedly decreased resistance to burn shock, thus explaining the decreased resistance of the nephrectomized animals in the experiments of longer duration. Finally, it was shown that there is no difference between nephrectomized and sham-nephrectomized animals if they are traumatized sufficiently to kill the animal before renal insufficiency becomes marked.

These results, demonstrating the ineffectiveness of the renal pressor system in burn shock, do not disprove the existence of the renal pressor system. However, it is clear that, in the type of trauma employed in these experiments, this system had no influence on survival. Whether or not the renal pressor system may have raised the blood pressure of our animals was not ascertained.

Renal excretory insufficiency has been found to occur quite frequently in shock, and, because of its deleterious effect, attempts should be made to control this factor in the treatment of patients in shock.

CONCLUSIONS

1. It was found that the renal pressor system has no influence on either mortality or survival time in burn shock.

2. Renal excretory insufficiency decreases the resistance of animals to burn shock. This factor should be considered in the treatment of patients in shock.

REFERENCES

1. Sapirstein, L. A., Ogden, E., and Southard, F. D., Jr.: Renin-Like Substance in Blood After Hemorrhage, Proc. Soc. Exper. Biol. & Med. **48**: 505, 1941.
2. Hamilton, A. S., and Collins, D. A.: Homeostatic Role of Renal Humoral Mechanism in Hemorrhage and Shock, Am. J. Physiol. **136**: 275, 1942.
3. Huidobro, F., and Braun-Menendez, E.: Secretion of Renin by Intact Kidney, Am. J. Physiol. **137**: 47, 1942.
4. Bahnson, H. T.: Role of the Kidneys in the Resistance of Rats to Hemorrhage, Am. J. Physiol. **140**: 416, 1943.
5. Prinzmetal, M., Hechter, O., Margoles, C., and Feigen, G.: Principle From Liver Effective Against Shock Due to Burns, J. A. M. A. **122**: 720, 1943; J. Clin. Investigation **23**: 795, 1944.
6. Megibow, R. S., Katz, L. N., and Rodbard, S.: Mechanism of Arterial Hypertension in Experimental Hydronephrosis, Am. J. M. Sc. **204**: 340, 1942.
7. Goldblatt, H., Kahn, J. R., and Lewis, H. A.: Studies on Experimental Hypertension, Experimental Observations on Hypertension Associated With Unilateral Renal Disease; Effect of Occlusion of Ureter on Experimental Hypertension Due to Unilateral Renal Ischemia, Arch. Surg. **43**: 327, 1941.

FURTHER STUDIES ON THE LIVER PRINCIPLE WHICH IS EFFECTIVE AGAINST BURN SHOCK

OSCAR HECHTER, PH.D., H. C. BERGMAN, PH.D., LEO SAPIRSTEIN, PH.D., ROY FISK, PH.D., GEORGE FEIGEN, B.S., AND MYRON PRINZMETAL, M.D.
LOS ANGELES, CALIF.

IN PREVIOUS work from this laboratory, it has been shown that there is a principle in liver extract which, when administered intraperitoneally or subcutaneously prior to thermal injury, significantly decreases the acute mortality and prolongs the survival time of rats and mice subjected to a standardized scalding procedure.[1] The present work was undertaken to ascertain whether liver exerts activity in types of shock other than that produced by scalding. We have, therefore, attempted to evaluate the action of liver extract in the shock produced by subjecting rats to temporary hind-leg ischemia; to an exudative inflammatory reaction, "medical shock"; and to hemorrhage. In addition, data are presented which demonstrate that liver extract is active in burn shock when administered by mouth prior to thermal injury.

EFFECT OF LIVER EXTRACT IN TOURNIQUET SHOCK

It has been regularly observed in tourniquet shock experiments that shock does not develop while the tourniquet is in place but occurs only after removal of the obstruction to blood flow.[2-4] The shock which develops after release of the tourniquets has been ascribed (a) to local fluid loss into the damaged limbs, for the application of casts to the ischemic limbs prevents shock;[3] and (b) to the release of toxic shock-producing factors formed in the ischemic areas into the general circulation.[2, 4] Since ischemic limbs of dogs may become infected, and air may accumulate under the skin,[3] the question whether the hypothetical toxic factor is primarily the result of the abnormal metabolism of ischemic tissues or is due to bacterial infection becomes important and has yet to be clearly answered.

After subjecting several hundred rats to tourniquet shock, it was observed that there are several complicating features, not mentioned in the literature, which are associated with this shock-producing procedure. These will be discussed separately.

Complicating Features.—

A. Hemorrhage from bites after removal of tourniquets: When rubber-band tourniquets are placed around the thighs of both hind legs,

From the Straus Research Laboratory, Cedars of Lebanon Hospital, and the University of Southern California Medical School.

Aided by grants from the Blanche May Selden Fund, the Martha Kirschner Haft Memorial Fund, F. Brice, Morton May, Walter Kirschner, and Mr. and Mrs. S. Marx.
Received for publication July 3, 1944.

the rats become exceedingly irritable. When such a rat is placed in a separate cage, it will bite its cyanotic limbs; or, if several rats are placed in the same cage, the animals will bite one another. The amount of blood loss suffered is nil when the circulation is occluded, but, upon release of the tourniquet and subsequent reactive hyperemia, the amount of hemorrhage through these bites may be considerable. When no precautions were taken to prevent this hemorrhage, it was observed in thirty cases that rats subjected to five-hour hind-leg ischemia regularly died after release of the tourniquets. When, however, biting, and, therefore hemorrhage, was prevented by sewing the rats' lips together, thirty animals whose hind-leg blood flow was obstructed for five hours showed only an 80 per cent mortality after release of the tourniquets. This indicates that removal of the extraneous hemorrhage factor permits survival that otherwise does not occur.

B. Effect of food and water: Since Hechter, Krohn, and Harris[5] previously reported zero mortality in ten rats subjected to five-hour tourniquet obstruction of both hind legs when the animals were allowed access to food and water, the effect of permitting animals to eat and drink after tourniquet removal was ascertained. In a series of sixty-four rats the mouth sutures were opened after tourniquet removal and the animals were allowed access to food and water, and it was found that the mortality was only 20 per cent. Remembering that the mortality was 80 per cent when the rats were not allowed access to food and water, this serves to indicate that markedly different results are obtainable, depending upon whether or not the animals are permitted to eat and drink.

C. Shocklike death without removal of the tourniquets: It was observed in six instances that the animals died in a shocklike state *before the tourniquets on the hind legs were removed.* In all of these cases, the hind legs were markedly cyanotic and were not edematous. Intra-aortic injection of concentrated trypan blue solution, shortly after the animals expired, produced staining of the tissues above, but not below, the tourniquet, demonstrating that the blood flow to these limbs was effectively occluded. The fact that death occurs in animals before the tourniquet is removed is not explicable in terms of local fluid loss, nor is it likely that death was due to toxic substances formed in the ischemic areas distal to the tourniquet. The possibility that the shock state developed as a result of muscle crushing above or beneath the tourniquet seems unlikely, for the area damaged in this fashion by a rubber band is relatively small, and previous work[6] has shown that large areas of muscle in rats may be traumatized without the development of shock.

D. Edema in occluded limbs before removal of obstruction: Although the rubber bands were tied tightly in all instances, it was observed that some animals developed significant edema in one or both of the obstructed limbs before the tourniquets were removed. This

suggests that occlusion of the arterial circulation by the tourniquet was not complete in these animals.

Effect of Liver Extract.—Taking the above factors into account, the effect of liver extract upon tourniquet shock was studied in the following manner: Etherized animals' lips were sewed together, and rubber-band tourniquets were tied tightly around both hind legs. Four and one-half hours later, the animals were divided into two groups. One group received 1 c.c. of 15-unit liver extract intraperitoneally per 100 grams of body weight; the other group received an equal volume of 0.5 per cent phenol solution by the same route. The animals were not allowed food or water. One-half hour after the injection, the ties were removed and survival observations were made. Four experiments, comprising the results on 155 rats, are shown in Table I; it is evident that liver extract treatment did not significantly alter the mortality of tourniquet shock in rats.

TABLE I

EFFECT OF LIVER EXTRACT ON THE MORTALITY PRODUCED BY TOURNIQUET SHOCK

EXPERIMENT	TREATMENT	NUMBER OF RATS	NUMBER LIVED	NUMBER DIED	MORTALITY (%)
1	Liver	12	6	6	50
	Control	11	6	5	45
2	Liver	19	4	15	79
	Control	19	4	15	79
3	Liver	19	15	4	21
	Control	19	12	7	37
4	Liver	28	8	20	72
	Control	30	11	19	63
Totals	Liver	78	33	45	58
	Control	77	33	46	60

The shock which follows tourniquet removal is apparently due to a complicated series of reactions which may be modified by many variables. In these experiments, factors such as hemorrhage from bites, nutrition and hydration, and environmental conditions were controlled; however, uncontrollable variables, such as edema, the unknown factor which occasionally led to death before tourniquet removal, and possible variable degrees of infection were still operative. The fact that liver extract was not effective in this form of shock demonstrates that shock-producing mechanisms which are not modified by liver extract treatment are responsible for death. However, the complexity of the tourniquet-shock syndrome permits no conclusions on this point, and it would be desirable to retest liver extract on tourniquet shock with all variables adequately controlled.

Attempts to Produce Shock by Exudative, Bacterial Inflammation.—In an attempt to simulate the shock which follows infectious states associated with a large amount of exudation, such as occurs in peritonitis, mice were injected intraperitoneally with pure cultures of either *Staphylococcus aureus,* pneumococci, or a suspension of feces. Although the

TABLE II

EFFECT OF LIVER EXTRACT UPON BACTERIAL SEPTICEMIA

ORGANISM	TREATMENT	NUMBER OF MICE	MEAN SURVIVAL TIME (HR.)	STANDARD ERROR
Staph. aureaus	Control	20	10.1	±2.3
	Liver	20	13.3	±2.7
Pneumococcus Type III	Control	57	25.3	±0.6
	Liver	57	22.3	±0.6
Suspension of feces	Control	80	19.8	±1.1
	Liver	80	19.9	±1.2

mice died after the injection of bacterial agents, contrary to our expectations, peritoneal exudates were not observed. The deaths were due to bacteremia; positive cultures were regularly obtained from the blood of the infected animals. The effect of liver extract treatment in this type of condition is shown in Table II; it will be seen that liver had no effect. Since little or no exudation was produced by these agents, no conclusions may be drawn regarding the action of liver extract in the shock which is associated with exudative inflammatory states. These data do indicate, however, that the shock associated with bacteremia induced by these organisms is not modified by liver treatment. It is of interest that it has recently been demonstrated that certain types of shock after muscle crushing experiments on dogs are of bacterial origin.[6] It would seem unlikely that liver extract, since it has no antibacterial action, would be effective in those types of shock in which bacteria are of primary importance.

Effect of Liver Extract After Hemorrhage.—It was observed that anesthetized rats could be bled more conveniently by severing the femoral artery with a sharp blade than by bleeding from the tail, by heart puncture, or by withdrawing blood from the femoral artery with a syringe. Using this technique, the degree of hemorrhage was ascertained by absorbing the blood on weighed cotton swabs.

The response of anesthetized rats to a single hemorrhage was found to depend not only upon the degree of exsanguination, but also upon the anesthetic employed. Thus, when ether was used, the degree of hemorrhage necessary to produce 50 per cent mortality varied from 2.7 to 3.2 per cent of the body weight. In nembutalized rats, however, hemorrhages ranging from as little as 2.3 to 2.5 per cent of the body weight proved to be uniformly fatal. Ogden has made similar observations.[7]

After bleeding etherized rats, the animals either (a) recovered immediately and survived indefinitely; (b) died within thirty minutes and showed, during this interval, symptoms of cardiovascular and respiratory distress (this is death due to acute exsanguination, and is not hemorrhagic shock); or (c) apparently recovered but then gradually declined and eventually died in a shocklike state. The effect of hemorrhage on nembutalized rats differed markedly from the results ob-

TABLE III

EFFECT OF ORALLY ADMINISTERED LIVER EXTRACT UPON SCALD SHOCK

ORAL WATER CONTROL				ORAL LIVER TREATMENT				
EXPERIMENT	NUMBER OF MICE	AVERAGE SURVIVAL TIME (HR.)	SURVIVORS (%)	NUMBER OF MICE	AVERAGE SURVIVAL TIME (HR.)	SURVIVORS (%)	INCREASE IN AVERAGE SURVIVAL TIME (%)	INCREASE IN SURVIVORS (%)
1	23	28.0	35	24	45.0	75	+61	+40
2	23	31.6	43	24	35.1	46	+11	+3
3	25	17.3	24	22	41.5	73	+14	+49
4	24	16.8	13	23	32.3	33	+92	+20
5	24	16.0	21	24	44.3	67	+177	+46
6	24	21.8	21	24	39.5	58	+81	+37
7*	20	20.4	15	21	42.4	67	+108	+52

*Oral 1 per cent sodium chloride control instead of oral water control.

tained on etherized rats in that death occurred after a prolonged period of decline which was similar to shock. It seemed clear, therefore, that the shocklike state observed in nembutalized rats was due in part to the nembutal. Since it seemed possible to attribute death under these conditions to an impairment by hemorrhage of the mechanisms involved in the removal or destruction of nembutal, as well as to hemorrhagic shock, we preferred not to use this method, although Engel, Winton, and Long[8] have made excellent observations regarding biochemical changes which occur in the shocklike state which occurs when nembutalized rats are subjected to hemorrhage.

In testing 15-unit liver extract on etherized rats it was observed that liver extract treatment did not alter the percentage mortality or the average survival time of the animals subjected to a single large hemorrhage. However, since the deaths which occurred were due to acute exsanguination, these data have little significance as regards the effect of liver in hemorrhagic shock.

It may be of interest that there was no effect of liver extract treatment upon the bleeding volume, as measured in etherized rats, using the aforementioned technique.

Effect of Orally Administered Liver Extract on Burn Shock.—The effect of orally administered liver extract on burn shock was evaluated, using the scalding method described previously in full detail.[1] Mice weighing approximately 20 grams were divided into two groups of at least twenty animals per group, and received, by stomach tube, either 1 c.c. of Lederle's 15-unit liver extract (which had been extracted with ether to remove the phenol preservative), or 1 c.c. of water. One-half hour later, the groups of mice were anesthetized with ether and scalded under identical conditions; the average survival time and the percentage mortality were ascertained. Six experiments of this type were performed; the usual condition of the scalding was an immersion period of ten seconds at 65° C. Experiment 7 was performed with a 1 per cent sodium chloride solution, instead of water, as a control.

Table III shows the results obtained on 325 mice. Examination of the data reveals that liver extract treatment by mouth decreased the mortality 32 per cent, and increased the survival time 98 per cent.

SUMMARY

These experiments demonstrate that liver extract, which has significant antiburn shock activity, either when administered parenterally, as in previous work,[1] or orally, as in the present study, is without comparable activity in the shock states which follow hind-leg ischemia or bacterial infection. It has been demonstrated that the mechanism of tourniquet shock in rats is complicated by several factors which are difficult to control. Before a final conclusion regarding the ineffectiveness of liver extract in this type of shock could be drawn, it would appear necessary that complicating factors be controlled. The nega-

tive results obtained with liver extract after acute exsanguination permit no conclusions to be drawn regarding liver activity in hemorrhagic shock.

The fact that liver is effective in burn shock, but not in tourniquet or bacterial shock, is further evidence for the concept that there are different mechanisms responsible for various types of shock, although all may give rise to a similar terminal picture. It further indicates that therapeutic measures must be evaluated individually for each type of shock, and that results obtained with one type of shock cannot be justifiably transferred to other types of shock.

CONCLUSIONS

1. Liver extract has significant antiburn shock activity when administered orally.

2. Liver extract has no therapeutic effect in certain types of bacteremia in mice.

3. Tourniquet shock in rats is due to the operation of complex mechanisms which are difficult to control.

4. Liver extract was found to be ineffective in tourniquet shock, and had no therapeutic effect in acute exsanguination.

REFERENCES

1. Prinzmetal, M., Hechter, O., Margoles, C., and Feigen, G.: A Principle From Liver Effective Against Shock Due to Burns, J. A. M. A. **122**: 720, 1943.
2. Allen, F. M.: Physical and Toxic Factors in Shock, Arch. Surg. **38**: 155, 1939.
3. Swingle, W. W., Remington, J. W., Kleinberg, W., Drill, V. A., and Eversole, W. J.: Experimental Study of Tourniquet as Method for Inducing Circulatory Failure in Dogs, Am. J. Physiol. **138**: 156, 1942.
4. Mylon, E., Winternitz, M. C., and de Süto Nagy, G. J.: Studies on Therapy in Traumatic Shock, Am. J. Physiol. **139**: 313, 1943.
5. Hechter, O., Krohn, L., and Harris, J.: Role of the Adrenals in Production of Traumatic Shock in Rats, Endocrinology **31**: 439, 1942.
6. Prinzmetal, M., Freed, S. C., and Kruger, H. E.: Pathogenesis and Treatment of Shock Resulting From Muscle Crushing, War Med. **5**: 74, 1944.
7. Ogden, E.: Personal communication.
8. Engel, F. L., Winton, M. G., and Long, C. N. H.: Biochemical Studies on Shock. Metabolism of Amino Acids and Carbohydrates During Hemorrhagic Shock in the Rat, J. Exper. Med. **77**: 397, 1943.

INEFFECTIVENESS OF ADRENOCORTICAL HORMONES, THIAMINE, ASCORBIC ACID, NUPERCAINE, AND POSTTRAUMATIC SERUM IN SHOCK DUE TO SCALDING BURNS

H. C. Bergman, Ph.D., D. D. Rosenfeld, A.B., Oscar Hechter, Ph.D., and Myron Prinzmetal, M.D.
Los Angeles, Calif.

WITHIN recent years, many substances have been reported to be therapeutically effective in certain types of experimental shock. Among these may be mentioned adrenocortical hormones, thiamine, ascorbic acid, nupercaine, and posttraumatic convalescent serum. Although some of these agents, on being tested in later work, have been found to be inactive by some workers, the effectiveness of other agents has been neither confirmed nor denied.

In previous work,[1] using the scalding method for evaluating therapeutic activity in burn shock, it was discovered that considerable group variation is encountered when apparently identical groups of untreated rats or mice were subjected to standardized thermal injury under identical conditions. These variations were observed in groups containing as many as twenty to thirty animals, and the differences between the untreated groups were statistically significant. It is apparent that, in any single experiment, the differences between a treated and a control group which appear to give rise to statistically significant results could be due to chance. In order to overcome this difficulty, the evaluation of therapeutic activity was made only after repeated testing.

Although it is not possible to state definitely that other methods which have been utilized to test antishock agents are subject to an equal degree of variability, the fact that the scalding method permits adequate control of variables such as the degree of thermal injury, body weight, strain, and environmental conditions both prior to and after thermal injury, which is not always obtainable with other methods, strongly suggests that they likewise may prove to possess significant variation equal to, if not greater than, that observed with the scalding method. Upon examining the literature, it would appear that insufficient attention has been given to the variations inherent in shock-producing procedures, and, in many instances, conclusions regarding therapeutic activity appear to have been derived from an insufficient number of tests. It is possible that some of the confusion and the controversial reports regarding therapeutic agents in shock may be explained in this way.

From the Straus Laboratory, Cedars of Lebanon Hospital, and the University of Southern California Medical School.

Aided by grants from the Blanche May Selden Fund, the Martha Kirschner Haft Memorial Fund, F. Brice, Morton May, Walter Kirschner, and Mr. and Mrs. S. Marx.
Received for publication July 3, 1944.

We therefore believed it necessary to ascertain whether or not agents which have been reported to possess therapeutic activity in shock are effective in the shock which follows scalding.

METHODS AND RESULTS

The scalding method utilized in these studies has been described previously in full detail.[1] Briefly, the method is as follows. Groups of twenty to thirty etherized rats or mice were submerged in scalding water of known temperature for definite periods of time. Rats weighing approximately 200 grams were scalded at 75° C. for fifteen seconds. The mice, weighing approximately 20 grams, were scalded at 65° C. for ten seconds. As in our previous work, the treated and control groups were derived from the same strain, with identical previous histories.

ADRENOCORTICAL HORMONES

Although it is definitely established that adrenalectomized animals have markedly lowered resistance to various types of trauma as compared with normal animals, and that treatment with adrenocortical hormones increases resistance toward normal,[2] the value of the adrenocortical hormones in the shock which occurs in intact, nonadrenalectomized animals has not been definitely ascertained.

Adrenal cortex extract has been reported to be useful in the treatment of toxic shock after intestinal obstruction[3] and the injection of the contents of a closed intestinal loop.[4, 5] Desoxycorticosterone produces no clear-cut effect in intestinal obstruction, although such treatment prevented the decline in plasma volume which is associated with this condition.[6] In the shock which follows intestinal trauma, it has been reported that cortical extract or corticosterones were effective, but that desoxycorticosterone was of no value.[7-9] Further, it has been observed that cortical extract therapy retards the decline in blood pressure which is associated with intestinal manipulation.[10] In hemorrhagic shock, it has been reported that cortical extract produces favorable results.[10] However, later observations in well-controlled experimentation have demonstrated the ineffectiveness of cortical hormone therapy in hemorrhagic shock.[11, 12] In the shock produced by venous occlusion of a hind leg, it has been reported that both cortical extract and desoxycorticosterone are effective when administered prophylactically.[13, 14] However, these results have not been confirmed.[15] It has been found that, although cortical extract was ineffective in preventing shock after venous occlusion, it did increase the efficacy of a salt infusion.[16]

Neither cortical extract nor desoxycorticosterone possesses therapeutic value in the shock induced in the dog by hind-leg trauma or by the release of tourniquets,[15] or in rats by tourniquet constriction.[17] In burn shock, there is evidence that cortical hormones are beneficial, for plasma electrolyte changes seem to be prevented,[18] and the efficacy of a plasma transfusion in increased.[19] However, further study of the latter point

indicates that cortical hormone therapy produces no significant effect.[20] In experimental burn shock in mice, Rosenthal[21] found that neither cortical extract nor desoxycorticosterone had significant antishock activity. Although much work has been done on the use of desoxycorticosterone and cortical hormones in the prevention and treatment of shock in man, the results are conflicting and difficult to evaluate because of the nature of this type of experimentation.

A. Effect of Desoxycorticosterone Acetate.—The effect of desoxycorticosterone acetate was tested in five trials on mice, using 158 mice, and in two trials on 87 rats. The dose of desoxycorticosterone was 5 and 2.5 mg. per 100 grams of body weight for rats and mice, respectively, and the drug was injected intraperitoneally one-half hour prior to thermal injury. The desoxycorticosterone used in these experiments was dissolved in sesame oil to make a solution containing 5 mg. per cubic centimeter. As a control for the desoxycorticosterone-treated animals, groups of rats and mice received an equivalent volume of sesame oil. The results are shown in Fig. 1, *A;* under the conditions of these experiments, desoxycorticosterone was without significant effect upon mortality in scald shock.

B. Effect of Adrenal Cortex Extract.—The effect of adrenal cortex extract treatment upon scald shock was studied in seven trials with 281 mice and three trials with 134 rats. The extract used was Cortin (Wilson), in a dose of 1 c.c. per 100 grams of body weight for both rats and mice. The extract was injected intraperitoneally one-half hour prior to scalding. Since the cortical extract is made up in saline, the control groups for the Cortin-treated animals received an equivalent volume of saline. The results of cortin treatment are shown in Fig. 1, *B.* It will be seen that adrenal cortical extract treatment had no therapeutic value.

THIAMINE

Thiamine has been reported to be therapeutically effective in hemorrhagic shock,[22] but this has been denied.[23] Further, thiamine does not possess therapeutic value in shock resulting from intestinal trauma.[23]

In our attempt to evaluate the effectiveness of thiamine in scald shock, eleven experiments, using a total of 475 mice, were performed. The mice in these experiments received 1 c.c. of saline, containing 10 mg. of thiamine chloride per 100 grams of body weight, by the intraperitoneal route, one-half hour prior to scalding. The control groups received saline in an equivalent amount.

The results, illustrated in Fig. 1, *C,* show that thiamine has slight or no significant therapeutic activity.

ASCORBIC ACID

Ungar[24] has reported that the administration of ascorbic acid in doses of 10 to 50 mg. per 100 grams of body weight is therapeutically

effective in traumatic shock. Similarly, it has been reported that ascorbic acid increases the resistance of dogs to acute hemorrhage.[25]

In our studies on the effect of ascorbic acid upon burn shock, six experiments, using a total of 297 mice, were performed. The dose of ascorbic acid was 50 mg. per 100 grams of body weight, and it was administered immediately after thermal trauma. In four trials, the ascorbic acid was injected intramuscularly in a volume of 0.1 c.c. of water. The ascorbic acid treated groups which received the substance by intramuscular injection were compared to groups which received no treatment; those that received ascorbic acid orally were compared to control groups which received 1 c.c. of water by mouth.

These data are shown in Fig. 1, *D*. The results indicate that ascorbic acid does not possess antiburn shock activity under the conditions of these experiments.

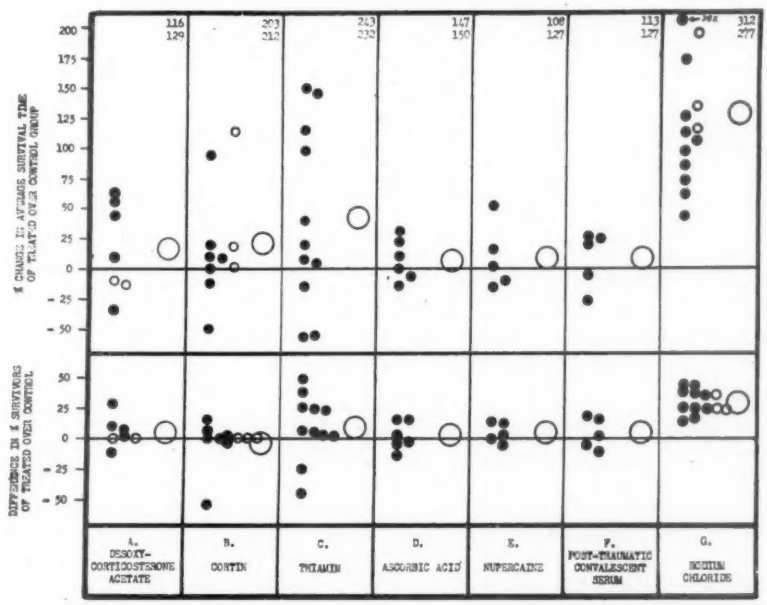


Fig. 1.—The effect of various therapeutic procedures on the response to thermal injury. Each dot and small circle represents the response of a group of at least twenty treated animals, as compared to an equivalent control group. The dots represent groups of mice, and the small circles, groups of rats. The large circles are means of the group responses. The figures in the upper right corner are the total number of treated animals over the total number of control animals.

NUPERCAINE

Stimulated by reports from Russia that the use of nupercaine for local anesthesia has resulted in a notable decrease in traumatic and surgical shock, Ungar[24] investigated the effects of local anesthetics upon experimental traumatic shock. He found that, although procaine was completely ineffective, nupercaine (4 mg. per kilogram of body weight),

injected either into the traumatized area or into a point distant from the injured area, proved therapeutically effective.

To ascertain the effect of nupercaine on scald shock, nupercaine was tested in five trials with 235 mice. The nupercaine was administered intramuscularly in a dose of 0.5 mg. per 100 grams of body weight, in a volume of 0.1 c.c. one-half hour after scalding. The nupercaine-treated mice were compared to controls which received no treatment.

The results are shown in Fig. 1, *E*, and illustrate the ineffectiveness of this treatment.

POSTTRAUMATIC CONVALESCENT SERUM

It has been shown that animals recovering from sublethal trauma due to a revolving wheel[26] or to temporary hind-leg ischemia[27] subsequently develop increased resistance and are able to withstand degrees of trauma that are usually fatal. Ungar[24] obtained similar results with the type of traumatic shock employed by him, but, in addition, he observed that the protective effect of previous trauma could be transferred from one animal to another and from one species to another by the injection of serum from traumatized animals.

To test the effect of posteonvalescent burn serum, etherized rats were subjected to scalding, and serum was obtained from the rats which were still alive forty-eight hours after thermal injury. These sera were pooled and stored in the ice chest until ready for use. This posttraumatic burn serum from rats was tested for specific antiburn shock activity in five trials, using 240 mice as the test animals. The dose of serum, administered approximately thirty to sixty minutes after scalding, was 1 c.c. per 100 grams of body weight. The treated animals were compared to control groups which received no treatment. These results are given in Fig. 1, *F*, which shows that treatment with posttraumatic serum from burned rats was ineffective in preventing shock in mice subjected to scalding.

For comparative purposes, the results obtained in previous studies with 5 c.c. per 100 grams of body weight of physiologic saline, administered one-half hour after trauma, are given in Fig. 1, *G*.

SUMMARY

Our results demonstrate that, under the conditions of these experiments, neither desoxycorticosterone acetate, adrenal cortical extract, thiamine, ascorbic acid, nupercaine, nor posttraumatic convalescent serum from burned rats possessed significant antiburn shock activity.

Of the agents tested, all seemed definitely ineffective, with the possible exception of thiamine, which, although it did not decrease mortality, did somewhat increase the average survival. It will be seen that this beneficial effect was not consistent. Therefore, we conclude that, although thiamine may be slightly effective in burn shock, its activity

is small as compared to the results obtained with a highly effective agent such as large volumes of saline solution or pretreatment with liver extract.[1]

Examination of the results with all of the agents under investigation reveals that, in any single test, using twenty animals per group, apparently positive results are obtainable; but, when the tests are repeated, and the results are evaluated in composite form, it is evident that the so-called positive effects are due to variability of the method. Although we cannot state definitely that similar variations are encountered in evaluating antishock activity with other methods, it does appear possible that some of the conflicting results regarding various agents in shock may be explicable in terms of variability factors which were not taken into account.

It is not intended to imply that our observations necessarily apply to other forms of shock, produced by other procedures, for there is now evidence that the cause and treatment of various types of shock may be fundamentally dissimilar.[28, 29]

CONCLUSIONS

The therapeutic activity against shock due to a standardized scalding burn in rats and mice has been ascertained for the following substances: desoxycorticosterone acetate, adrenal cortical extract, thiamine, ascorbic acid, nupercaine, and posttraumatic convalescent serum. It was found that none of these agents possessed significant antiscald shock activity when tested on a sufficient number of animals under controlled conditions.

REFERENCES

1. Prinzmetal, M., Hechter, O., Margoles, C., and Feigen, G.: A Principle From Liver Effective Against Shock Due to Burns, J. A. M. A. **122**: 720, 1943, Ibid, J. Clin. Investigation **23**: 795, 1944.
2. Swingle, W. W., and Remington, J. W.: The Role of the Adrenal Cortex in Physiological Processes, Physiol. Rev. **24**: 89, 1944.
3. Wohl, M. G., Burns, J. C., and Pfeiffer, G.: High Intestinal Obstruction in Dog Treated With Extract of Adrenal Cortex, Proc. Soc. Exper. Biol. & Med. **36**: 549, 1937.
4. Heuer, G. J., and Andrus, W. D.: The Effect of Adrenal Cortex Extract in Controlling Shock Following the Injection of Aqueous Extracts of Closed Intestinal Loops, Ann. Surg. **100**: 743, 1934.
5. Laufman, H., and Freed, S. C.: Observations on the Transudate in Intestinal Strangulation: I. The Effect of Adrenal Cortical Extract on Its Toxicity, Surg., Gynec. and Obst. **77**: 605, 1943.
6. Fine, J., Fuchs, F., and Mark, J.: Effect of Desoxycorticosterone on Plasma Volume in Intestinal Obstruction, Proc. Soc. Exper. Biol. & Med. **43**: 514, 1940.
7. Selye, H., and Dosne, C.: Treatment of Wound Shock With Corticosterone, Lancet **2**: 70, 1940.
8. Selye, H., Dosne, C., Bassett, L., and Whittaker, J.: On the Therapeutic Value of Adrenal Cortical Hormones in Traumatic Shock and Allied Conditions, Canad. M. A. J. **43**: 1, 1940.
9. Weil, P. G., Rose, B., and Browne, J. S. L.: Reduction of Mortality From Experimental Traumatic Shock With Adrenal Cortical Substances, Canad. M. A. J. **43**: 8, 1940.
10. Helfrich, L. S., Cassels, W. H., and Cole, W. H.: Cortical Extract in Treatment of Shock; Preliminary Report, Am. J. Surg. **55**: 410, 1942.

11. Fine, J., Fischmann, J., and Frank, H. A.: The Effect of Adrenal Cortical Hormones in Hemorrhage and Shock, Surgery **12**: 1, 1942.
12. Huizenga, K. A., Brofman, B. L., and Wiggers, C. J.: Ineffectiveness of Adreno-Cortical Preparations in Standardized Hemorrhagic Shock, Proc. Soc. Exper. Biol. & Med. **52**: 77, 1943.
13. Katz, L. N., Killian, S. T., Asher, R., and Perlow, S.: Prophylactic Action of Desoxycorticosterone in Shock Due to Massive Venous Thrombosis, Am. J. Physiol. **137**: 79, 1942.
14. Shleser, I. H., and Asher, R.: Efficacy of Adrenal Cortical Extract and of Paredrine in Prevention of Experimental Shock Following Venous Occlusion of Limb, Am. J. Physiol. **138**: 1, 1942.
15. Swingle, W. W., Overman, R. R., Remington, J. W., Kleinberg, W., and Eversole, W. J.: Ineffectiveness of Adrenal Cortex Preparations in Treatment of Experimental Shock in Non-Adrenalectomized Dogs, Am. J. Physiol. **139**: 481, 1943.
16. Bourque, J. E., Haterius, H. O., and Glassco, E.: Treatment of Circulatory Collapse of Experimental Venous Occlusion; Use of Adrenal Cortical Extract and Saline Solutions, Proc. Soc. Exper. Biol. & Med. **52**: 313, 1943.
17. Ingle, D. J.: Survival of Non-Adrenalectomized Rats in Shock With and Without Adrenal Cortical Hormone Treatment, Am. J. Physiol. **139**: 460, 1943.
18. Wilson, W. C., MacGregor, A. R., and Stewart, C. P.: Clinical Course and Pathology of Burns and Scalds Under Modern Methods of Treatment, Brit. J. Surg. **25**: 826, 1938.
19. Rhoads, J. E., Wolff, W. A., and Lee, W. E.: Use of Adrenal Cortical Extract in Treatment of Traumatic Shock of Burns, Ann. Surg. **113**: 955, 1941.
20. Rhoads, J. E., Wolff, W. A., Saltonstall, H., and Lee, W. E.: Further Experiences With Adrenal Cortical Extract in the Treatment of Burn Shock, Ann. Surg. **118**: 982, 1943.
21. Rosenthal, S. M.: Experimental Chemotherapy of Burns and Shock; Effects of Systemic Therapy on Early Mortality, Pub. Health Rep. **58**: 513, 1943.
22. Govier, W. M., and Greer, C. M.: Studies on Shock Induced by Hemorrhage; Effect of Thiamin on Survival Time, J. Pharmacol. & Exper. Therap. **72**: 317, 1941.
23. Maycock, W. d'A.: Effect of Vitamin B_1 on Survival Time After Hemorrhage and Application of Cold, Quart. J. Exper. Physiol. **32**: 29, 1943.
24. Ungar, G.: Experimental Traumatic "Shock"; Factors Affecting Mortality and Effect of Therapeutic Agents (Ascorbic Acid and Nupercaine), Lancet **1**: 421, 1943.
25. Stewart, C. P., Leanmonth, J. R., and Pollock, G. A.: Intravenous Ascorbic Acid in Experimental Acute Hemorrhage, Lancet **1**: 818, 1941.
26. Noble, R. L.: Development of Resistance by Rats and Guinea Pigs to Amounts of Trauma Usually Fatal, Am. J. Physiol. **138**: 346, 1943.
27. Green, H. N.: Shock-Producing Factor (s) From Striated Muscle; Isolation and Biological Properties, Lancet **2**: 147, 1943.
28. Blalock, A.: Consideration of the Present Status of the Shock Problem, Surgery **14**: 487, 1943.
29. Prinzmetal, M., Freed, S. C., and Kruger, H. E.: The Pathogenesis and Treatment of Shock Resulting From Crushing of Muscle, War Med. **5**: 74, 1944.

EFFECT OF SHORT-TERM NUTRITIONAL STRESS UPON RESISTANCE TO SCALD SHOCK

H. C. Bergman, Ph.D., Oscar Hechter, Ph.D., and
Myron Prinzmetal, M.D.
Los Angeles, Calif.

IN THE majority of instances, studies on experimental shock have been conducted with animals housed under protected laboratory conditions and receiving an adequate diet. However, shock as it occurs under combat conditions may be preceded by a wide variety of physiologic stresses, among which may be mentioned malnutrition and dehydration. The question arises as to whether preliminary subjection to short-term stress influences the ability of the organism to resist shock. In this report, studies are presented concerning the influence of short-term nutritional stress, such as fasting, water deprivation, and adequate dietary regimes upon resistance to the shock which follows thermal injury.

The details of the scalding method have been described in a previous report.[1] For the present experiments, groups of twenty or more mice of the same strain, weight range, and sex distribution were either deprived of food or given the particular diet for forty-eight hours prior to scalding. During this period, water was allowed ad libitum except for the water deprivation study. Purina fox chow was used as the complete diet for comparison with other diets. The mice, anesthetized with ether, were scalded at 65° C. for ten seconds. During the following forty-eight hours, no food or water was allowed. All mice alive at the end of this period were assigned an arbitrary survival time of forty-eight hours.

Forty-eight-Hour Fast.—To ascertain the influence of a forty-eight-hour fast upon resistance to scald shock, twelve experiments, comprising 717 mice, were performed, in which groups of fasted mice were anesthetized with ether, scalded, and compared to similarly treated groups which were fed fox chow ad libitum. Both groups had access to water up to the time of scalding. This forty-eight-hour fast decreased body weight approximately 15 to 17 per cent.

Forty-eight-Hour Fast, No Water.—The effect of water deprivation upon resistance to scald shock was studied in four experiments, using a total of 179 mice. Groups allowed neither food nor water for forty-eight hours were compared to groups allowed access to drinking water but no food. The dehydrated mice lost 17.5 to 20 per cent of their initial body weight, as compared to 15 to 17.5 per cent reduction for the mice which were allowed water but no food.

From the Straus Laboratory, Cedars of Lebanon Hospital, and the University of Southern California Medical School.

Aided by grants from the Blanche May Selden Fund, the Martha Kirschner Haft Memorial Fund, F. Brice, Morton May, Walter Kirschner, and Mr. and Mrs. S. Marx.

Received for publication July 3, 1944.

EXPERIMENTS WITH SHORT-TERM INADEQUATE DIET

The effect of incomplete dietary regimes for two days upon resistance to scald shock was ascertained by comparing the survival after thermal injury of groups of mice fed several types of inadequate diets with control groups of mice fed the complete diet of Purina fox chow. All of these animals received water ad libitum. These experiments are summarized below.

Protein.—Casein (S.M.A. Corporation) was given ad libitum to five groups of mice, comprising 328 animals, for forty-eight hours. In addition, 1 c.c. of protein digest (Amigen, Mead Johnson), containing 10 per cent amino acids, was administered by stomach tube twenty-four and forty-eight hours prior to scalding. These mice lost approximately 15 per cent of their initial body weight.

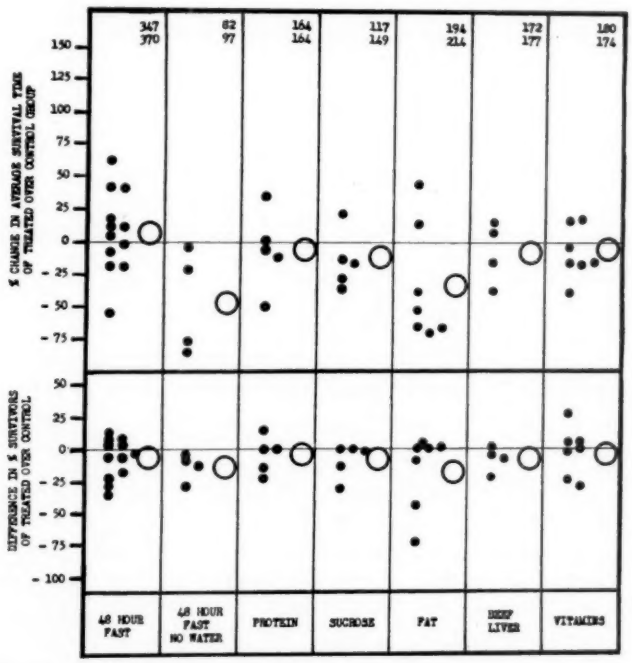


Fig. 1.—The effect of various short-term procedures on the response of mice to thermal injury. Each dot represents the response of a group of at least twenty treated mice, as compared to a control group containing an equivalent number of mice. The large circles are means of the group responses. The figures in the upper right corner are the total number of treated animals over the total number of control animals.

Sucrose.—Sucrose was given ad libitum to five groups of mice (total, 266) for forty-eight hours, during which time the average loss of body weight was approximately 10 per cent.

Fat.—A total of 408 mice were used. In three experiments, lard was fed ad libitum, and in four other experiments sesame oil was given by mouth in 0.5 to 1 c.c. doses twenty-four and forty-eight hours prior to scalding. The fat-fed animals lost from 15 to 20 per cent of their initial body weight. At the termination of the experiments, gross examination revealed that the livers of these animals were filled with fat.

Beef Liver.—Advantage was taken of the fact that mice fed nothing but minced beef liver for two days lost approximately 15 per cent of their initial weight. The effect of this diet of mixed composition, which does not maintain body weight, was studied in four experiments on 349 mice as regards resistance to scald shock.

Vitamins.—Seven groups of mice (total, 354) were given, by mouth, one drop of Haliver oil (Abbott) and 1 c.c. of a solution containing 2 mg. of thiamine chloride, 2 mg. of ascorbic acid, 0.4 mg. of nicotinic acid, 0.4 mg. of pyridoxine, 0.04 mg. of riboflavin, and 0.006 mg. of pantothenic acid twenty-four and forty-eight hours prior to scalding. Comparisons were made with mice which received 1 c.c. of water. Access to water was allowed in both cases. These groups lost approximately 15 to 20 per cent of their initial body weight.

Fig. 1 is a summary of the results obtained. Although there was a marked loss of body weight, it will be seen that neither a forty-eight-hour fast nor a previous short-term diet consisting solely of protein, carbohydrate, or fat had a significant influence on the mortality or the average survival time of mice subjected to thermal injury. Similarly, a diet of nothing but whole liver, which caused loss of weight, did not lower resistance.* Further, it was observed that large doses of a mixture of vitamins A and D, plus ascorbic acid, thiamine, and several members of the B complex group, did not modify the response to scald shock. The results with mice which were not allowed access to water for forty-eight hours show that there is a tendency toward lowered resistance, as evidenced by the decrease in the survival time after scalding.

It appears that, when dehydration is prevented, short periods of stress due to fasting or a poor nutritional regimen do not significantly reduce the resistance of mice subjected to thermal injury.

REFERENCE

1. A. Prinzmetal, M., Hechter, O., Margoles, C., and Feigen, G.: A Principle From Liver Effective Against Shock Due to Burns, J. A. M. A. **122**: 720, 1943. B. Ibid., J. Clin. Investigation **23**: 795, 1944.

*The amount of whole liver ingested in these feeding experiments was considerably less than the amounts of liver required to produce liver extracts with antiburn shock activity.[1]

UROLOGIC DISEASE AS A CAUSE OF HYPERTENSION

MAURICE M. RATH, PH.D., M.D., AND HENRY I. RUSSEK, M.D.
STATEN ISLAND, N. Y.

THAT urologic disease or surgical conditions of the urinary tract, such as lithiasis, hydronephrosis, and pyelonephritis, may be causally related to hypertension in man seems possible.

The current clinical interest in this problem was aroused by the experimental studies of Goldblatt, in 1934, and of others in later years. Goldblatt, et al.,[1] recently pointed out that human hypertension associated with unilateral renal disease, such as chronic pyelonephritis or other conditions which disturb renal hemodynamics, has been recognized as an entity. The damage to intrarenal blood vessels resulting from such a disease is considered as favoring the secretion of a pressor substance, and hence as being a causative factor in the hyperpiesis. But others[2, 3] contend it has not been established that arterial and arteriolar changes always precede human hypertension. Whether vascular disease in the kidney is the cause, result, or both, of elevated blood pressure has not been definitely answered. Investigators have reported finding extensive histologic changes in renal vessels without hypertension, on the one hand, and hypertension without perceptible vascular changes, on the other.

Can definite evidence be found to substantiate the belief that urologic disease and high blood pressure are interrelated? Investigators have approached the problem along two avenues. Some have studied the incidence of hypertension in cases of known urologic disease, and others have reported the incidence of urologic disease among patients with hypertension.

The work of Weiss and Parker[4] has often been quoted to support the claim that pyelonephritis and hypertension are interrelated. These authors studied the kidneys of patients with pyelonephritis and high blood pressure, and believed their evidence indicated that hypertension in this condition depends on obliterative arteriolar lesions brought about by the infection. They admitted, however, that their method of selecting cases was such that the data were not suited to statistical analysis.

Barney and Suby[5] studied 305 cases of pyelonephritis and hydronephrosis on the Urological Service of the Massachusetts General Hospital, in 25 per cent of which there was hypertension. These authors employed a systolic blood pressure of 140 mm. Hg or more as the criterion for hypertension. Inasmuch as no control series was reported, the significance of their observations is not clear. Crabtree, Chaset, and Chaset,[6]

From the U. S. Marine Hospital.
Published with the permission of the Surgeon General of the United States Public Health Service.
Received for publication July 5, 1944.

found that, of 150 consecutive patients with severe unilateral renal damage, 9.3 per cent showed an elevated blood pressure. They considered 150 mm. Hg, systolic, and 100 mm. Hg, diastolic, as hypertensive levels. These authors concluded that their patients with renal disease had a slightly lower average blood pressure than normal subjects. They employed for their control a series reported by another investigator. Abeshouse[7] observed that hypertension was present prior to operation in 17.3 per cent of 167 nephrectomized patients with unilateral renal disease (neoplasm, pyelonephritis, calculus, tuberculosis, etc.). Morlock and Horton[8] reported that 40 per cent of 335 patients with hypernephroma had hypertension. About 70 per cent were between the ages of 45 and 65 years. Among 124 patients with other types of renal tumors (sarcomas, squamous cell carcinomas, etc.), 46 per cent had hypertensive blood pressure levels. In this work they considered a systolic blood pressure of 140 mm. Hg or more as hypertensive. They found that no consistent alteration in blood pressure followed removal of the tumors.

Is it not possible for any comparably large group of persons to show a comparable incidence of hypertension, even though no renal disease is apparent or suspected? Of a random control group of 975 consecutive cases studied at the Mayo Clinic by Braasch and Jacobson,[9] 20 per cent were found to have hypertension (systolic, 145 mm. Hg, or diastolic, 90 mm. Hg, or more). Similarly, a study by Shure[10] revealed that 34.9 per cent of 947 persons chosen at random had blood pressures of 150/95 or more.

Of 1,684 patients with "surgical kidney" (adenocarcinoma, pyelonephritis, hydronephrosis, calculus, etc.), Braasch and his co-workers[11] found that 18.6 per cent had preoperative hypertension. In another study, limited to pyelonephritis, they[9] reported an incidence of hypertension of 26 per cent among 180 patients. Among persons 50 years of age or over, approximately the same proportion of both the pyelonephritic group and the control group exhibited high blood pressure, according to their definition, whereas, among the 119 test subjects under 50 years of age the incidence of hypertension associated with pyelonephritis was 16 per cent, as compared to 9.1 per cent of 606 members of the control group. As the authors point out, the incidence of hypertension was approximately twice as great in the younger pyelonephritic patients as in the younger control group. However, we have found that the standard error of the difference between these two values is 3.6, which makes the actual difference of doubtful statistical importance. In other words, "twice as much" in this instance is not impressive. Rather, it is a difference of 6.9 per cent (16 minus 9.1) that concerns us, and this deviation could well be the result of chance.

Braasch and Wood[12] more recently have reported on 70 cases of primary perinephritis or perinephritic abscess. The mean age of the pa-

tients was 38 years. Only 4.2 per cent had an elevated blood pressure, and this, they point out, is an incidence of hypertension of less than half that in the random sample of patients under 50 years of age at the Mayo Clinic. Our analysis of their data shows that the difference between 9.1 and 4.2 per cent, divided by its standard error, yields a value of 1.9, which is slightly lower than the level commonly accepted as a measure of significance.

Shure[10] found that the incidence of hypertension (150/95 or over) in a control group of 947 persons chosen at random was 34.9 per cent, as compared to 44.4 per cent of 290 patients with pyelonephritis. He concluded that in cases of bilateral pyelonephritis there appears to be a distinct increase in the incidence of hypertension. This difference seems to be statistically significant from a consideration of the standard error.

A compilation of the data presented in the papers just discussed would reveal that "hypertension" was present in 828, or 25 per cent, of 3,305 urologic cases; in contrast, 526, or 27 per cent, of 1,922 subjects serving as controls exhibited "hypertension." Obviously, these figures have little or no value because the same criteria were not utilized by the respective authors.

The incidence of urologic disease among hypertensive patients also has been studied by various investigators. Palmer and his co-workers[13] reported that 22 per cent of their 212 hypertensive patients had urinary tract disease, as diagnosed urographically. Pressures of 150/100 or over were regarded by these authors as being in the hypertensive range. Ratliff and Conger[14] found that, of 340 hypertensive patients who were not suspected of having urologic disease, 32, or 9.42 per cent, exhibited renal disease, as revealed by excretion and retrograde pyelographic study. They employed a level of 140/90 to divide hypertensive from normal subjects. In the course of routine examination, hypertension was found by Braasch[15] in 4,000 cases in which clinical evidence of a nonnephritic renal lesion was discovered in 100, or 2.5 per cent. This author refers to the so-called surgical kidney as "an etiologic factor of hypertension which has been definitely proved by clinical experience—."

Schroeder and Steele[16] studied 250 cases of essential hypertension, in 113 (45 per cent) of which there was some form of organic renal disease. They did not clearly state their criteria for hypertension. In another series of 100 cases of hypertension reported by Williams and Harrison,[17] 30 per cent of the patients had urologic disease. These workers employed a level of 150/100 in the segregation of hypertensives from normals. Wosika and Maher[18] reviewed the records of 574 hypertensive patients who were free from glomerulonephritis, and found that 101, or 16.8 per cent, had various surgical forms of urinary tract disease.

Wosika, Jung, and Maher[19] reported that, in a large series of postmortem protocols, 27.4 per cent of a group with normal blood pressure, and 40 per cent of a hypertensive group, had urologic disease. They applied the chi square test to their data and considered that the difference between the groups had statistical significance. These authors conclude, "one may safely infer that a patient with hypertension is more likely to have urologic disease than is a patient without hypertension." Although these results appear impressive, it should be emphasized that what Wosika and his associates term "hypertension" is actually elevation of the systolic blood pressure (140 mm. Hg or more). In their opinion, the systolic level appears to be an adequate criterion for hypertension. They state further that, "including the diastolic pressure . . . is not only impractical clinically, but it obscures the logic, complicates the mathematics, and attenuates the statistical analysis." Because of these remarks and for reasons to be discussed we are not convinced that the results of their study are valid.

If one attempts to compile the data supplied by these seven papers it would appear that, of a total of 6,044 so-called hypertensive patients, 650, or 10.7 per cent, exhibited evidence of urologic disease. In the nonhypertensive control group collected by Wosika and his associates, however, 167 of 611 subjects, or 27.4 per cent, proved to have urologic conditions. Judging from these collected figures, the incidence of urologic disease in a large group of "hypertensive" patients appears no greater (if not actually less) than the incidence in a group of nonhypertensive patients. Here again, such compiled data must be considered with caution because the blood pressure criteria, as well as control methods, varied among the different investigators. These diverse observations of independent workers who report an incidence of urologic disease among hypertensive subjects ranging from 2.5 to 45 per cent clearly indicate that the problem has not yet been solved.

In the studies we have briefly reviewed we noted that in some instances investigators failed to employ a control series for comparison. Consequently, evaluation of their results is difficult. Other workers have made little or no attempt to interpret statistically the results of their studies. Unless the reliability of a difference between two sets of figures has been estimated, inferences cannot be safely drawn from that difference. Without the employment of even some simple probability test, we may err by building arguments on a foundation which is insecure because of improper sampling. But even prior to the application of statistical methods, it must be ascertained that the basic material is free from fault.

A great source of confusion is derived from the diversity of opinion regarding the definition of hypertension. Some authors have used only the systolic blood pressure as a criterion of hypertension. Consequently, the same significance was assigned to all elevations of systolic blood pressure, regardless of the accompanying level of diastolic pres-

sure. The erroneous conclusions which may follow such a classification in groups of older persons are apparent when one considers that systolic hypertension (high systolic, with normal or low diastolic, pressure) has its own distinct mechanism, and is caused by arteriosclerosis of the aorta and its larger branches. Clinicians are agreed that this form of elevation of blood pressure has no relation to essential or renal hypertension. One of us,[20] furthermore, has demonstrated that the incidence of systolic hypertension mounts sharply after the sixth decade. This consideration demands that no age discrepancies exist between test and control series. Without such careful control of the age factor, the employment of systolic pressure exclusively may lead to unjustified assumptions. There is strong evidence, moreover, that the diastolic pressure is a more reliable index than systolic pressure in the recognition of hypertensive disease.[20, 21]

In accordance with the foregoing concepts, we have studied a series of urologic and control cases in an attempt to add to the present knowledge concerning the relationship between arterial pressure and surgical diseases of the urinary tract.

MATERIAL

A group of 357 merchant seamen and coastguardmen served as test subjects. The three chief conditions, singly or in combination, for which they were hospitalized were nephrolithiasis or ureterolithiasis, hydronephrosis, and prostatic hypertrophy. A smaller number of the men were suffering from pyelitis, pyelonephritis, bladder stone, ureteral stricture, and pyonephrosis. All diagnoses were confirmed by roentgenographic, cystoscopic, or operative procedures. Of the patients with prostatic disease approximately 15 per cent had acute retention when they were admitted to the hospital. The average age of the 357 patients was 44.3 years.

Serving as controls were 654 patients selected at random, all of whom were merchant seamen or coastguardmen of the same habits and background as the urologic patients, but were hospitalized for other reasons. Their average age was 46.4 years. The difference between the average age of the control and test groups was not statistically significant; T* was 1.9.

RESULTS

Study of Table I will show that the urologic patients as a whole, or when considered by age groups, had no higher average blood pressure than the control subjects. In fact, the data reveal a slightly, but significantly, higher average systolic pressure in the majority of the con-

*T is the difference divided by the standard error of that difference, and was calculated, when applied to means, by Formula A, and by Formula B when applied to percentages. A T level of 2.5 or more was adopted as a measure of statistical significance.

$$(A)\quad \frac{M_1 - M_2}{\sqrt{\frac{S.D._1^2}{n_1} + \frac{S.D._2^2}{n_2}}} \qquad (B)\quad \frac{P_1 - P_2}{\sqrt{\frac{p_1q_1}{n_1} + \frac{p_2q_2}{n_2}}}$$

where $M_1 - M_2$ is the difference between means; S.D., standard error; n, number of cases; $p_1 - p_2$, difference between proportions; p, percentage in one sample having the characteristic; q, percentage in same sample not having the characteristic.

trol groups. The urologic patients had average systolic blood pressures which were higher than the controls only in the 20 to 29 and 50 to 59 age ranges, but these differences were not statistically significant, as evidenced by T values of 0.8 and 0.5, respectively. Analysis of the diastolic blood pressures similarly indicates no correlation between urologic disease and elevated levels.

Table II shows the relation of age to the incidence of various blood pressure levels in control and urologic groups. All pressures below 145/95 were classified as normal; systolic pressures of 145 or above, with diastolic pressures under 95, were regarded as indicative of systolic hypertension; when the diastolic pressure was 95 or above, diastolic hypertension was said to be present.

From the data in Table II it is apparent that the minor differences between test and control groups can readily be explained on chance occurrence. The influence of age upon arterial pressure is clearly demonstrated by Tables I and II. With advance in age there is not only a rise in average systolic and diastolic blood pressure in both urologic and control groups, but also a concomitant increase in the incidence of systolic hypertension and of diastolic hypertension. Conversely, there is a diminishing frequency of normal blood pressure with advancing years. These trends are made more evident by the comparison between "younger" (10 to 49 years) and "older" (50 to 89 years) persons. That the differences between these two major groups are significant is demonstrated by T values ranging from 3.4 to 17.9.

When the urologic patients are divided into the three main classifications, hydronephrosis, kidney and ureteral lithiasis, and prostatic hypertrophy, and their average blood pressures are compared with controls of corresponding age, the results again indicate that the differences between the means are likely due to chance (Table III). The pyelonephritis, bladder stone, pyonephrosis, and pyelitis groups were too small to be listed in Table III for statistical comparison. A discrepancy will be noted between the total number of cases in the three groups of urologic cases in this table, as compared with the test group described in Tables I and II. This is explained by the fact that some of the patients had a combination of these urologic conditions.

DISCUSSION

To ascertain whether urologic hypertension exists as an entity, we have compared a group of patients who had surgical conditions of the urinary tract with a nonurologic series. In this study we attempted to control such factors as age, sex, and occupation in both groups. We already have pointed out that the use of systolic blood pressure as the only criterion for dividing normal from hypertensive levels may be a serious source of error, in view of the fact that a high incidence of systolic hypertension normally occurs in older persons (Table II). Hence, we have broken down our data according to age and average systolic and diastolic pressure, and according to the percentage incidence

TABLE I

AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURES AMONG UROLOGIC AND CONTROL CASES

AGE (YRS.)	TOTAL NUMBER OF CASES		AVERAGE SYSTOLIC BLOOD PRESSURE			AVERAGE DIASTOLIC BLOOD PRESSURE		
	UROLOGIC	CONTROL	UROLOGIC (MM.HG)	CONTROL (MM.HG)	T*	UROLOGIC (MM.HG)	CONTROL (MM.HG)	T*
10 to 19	7	38	113.56	125.78	a	70.85	82.1	a
20 to 29	68	160	123.52	120.25	0.8	78.38	81.2	1.9
30 to 39	79	86	122.72	130.24	3.4	80.32	83.3	1.7
40 to 49	75	85	127.54	134.3	2.2	82.6	86.1	2.2
50 to 59	58	63	139.82	137.8	0.5	87.94	85.31	1.2
60 to 69	57	117	146.23	153.2	2.3	90.09	89.1	0.4
70 to 79	13	104	142.0	160.0	a	80.84	88.5	a
80 to 89	0	1	–	(125)	–	–	(75)	–
10 to 49	229	369	124.84 ± 1.03[b]	129.16 ± 0.77	3.2	80.34 ± 0.67	82.32 ± 0.64	2.1
50 to 89	128	289	142.6 ± 2.10	152.16 ± 0.98	3.8	86.46 ± 1.21	86.8 ± 0.96	0.2
10 to 89	357	645	131.9 ± 1.13	139.8 ± 0.82	5.6	82.9 ± 0.64	85.09 ± 0.54	2.5

a = Too few cases for statistical comparison.
b = These ± values represent standard errors.
*See footnote on page 518.

TABLE II

PERCENTAGE INCIDENCE OF NORMAL BLOOD PRESSURE, SYSTOLIC HYPERTENSION, AND DIASTOLIC HYPERTENSION AMONG UROLOGIC AND CONTROL SUBJECTS

AGE (YRS.)	NORMAL BLOOD PRESSURE			SYSTOLIC HYPERTENSION			DIASTOLIC HYPERTENSION		
	UROLOGIC (%)	CONTROL (%)	T*	UROLOGIC (%)	CONTROL (%)	T*	UROLOGIC (%)	CONTROL (%)	T*
10 to 19	100	100	–	0	0	–	0	0	–
20 to 29	91.1	94.3	0.8	2.9	2.5	1.0	5.9	3.12	0.3
30 to 39	93.7	90.2	0.8	2.5	4.6	0.7	3.8	5.81	0.6
40 to 49	85.3	84.7	0.1	8.0	5.8	0.5	6.6	11.76	1.1
50 to 59	65.5	74.6	1.1	18.9	14.2	0.8	15.5	11.11	0.7
60 to 69	46.6	42.7	0.5	31.5	33.3	0.2	22.7	23.93	0.1
70 to 79	61.6	31.7	a	30.7	42.3	a	7.6	25.00	a
80 to 89	–	(1 case)	–	0	0	–	0	0	–
10 to 49	90.3	91.0	0.2	4.36	3.52	0.6	5.24	5.41	0.1
50 to 89	56.2	45.9	1.9	25.78	32.28	1.3	17.96	21.75	0.92
10 to 89	78.1	71.46	2.3	12.04	16.05	1.8	9.8	12.53	1.3

Normal blood pressure, 144/94 or below.
Systolic hypertension, 145 mm. Hg systolic or over, with diastolic 94 mm. Hg or below.
Diastolic hypertension, 95 mm. Hg diastolic or over.
a = Too few cases for statistical analysis.
*See footnote on page 518.

of normal blood pressure, systolic hypertension, and diastolic hypertension. We were unable to demonstrate an association between urologic disease and hypertension. We found, as others previously have observed, that the age factor has a definite influence on systolic and diastolic blood pressure. Our data show that increments in arterial pressure occur with age in our test and control groups. The percentage incidence of systolic hypertension in the younger urologic and control series was 4.3 and 3.5 per cent, respectively, as compared with 25.7 and 32.2 per cent, respectively, in the older subjects (50 years and over). The percentage incidence of diastolic hypertension in the younger urologic and control series was 5.2 and 5.4 per cent, respectively, in comparison to 17.9 and 21.7 per cent in the older subjects. Of the entire test group, 12 per cent had systolic hypertension, and 9.8 per cent, diastolic hypertension. The respective values in the control series were 16 and 12.5 per cent.

TABLE III

AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURE OF PATIENTS WITH HYDRONEPHROSIS, PROSTATIC HYPERTROPHY, AND RENAL AND URETERAL LITHIASIS, COMPARED WITH CONTROL SUBJECTS OF THE SAME AGE

	NUMBER OF CASES	AVERAGE AGE (YRS.)	AVERAGE SYSTOLIC BLOOD PRESSURE (MM. HG)	T*	AVERAGE DIASTOLIC BLOOD PRESSURE (MM. HG)	T*
Controls	86	30 to 39 (35)	130.24		83.3	
Hydronephrosis	122	38.15	126.0	2.0	81.53	0.5
Lithiasis	156	39.21	129.36	0.5	82.18	0.8
Controls	63	50 to 59 (55)	137.81		85.31	
Prostatic Hypertrophy	122	56.06	142.06	1.2	86.97	0.9

*See footnote on page 518.

Bicknell,[22] in discussing the incidence of hypertension in patients with "surgical" kidneys, considered that the age factor appears to have more influence than any other. He admitted, for instance, that hypertension is common in patients with hypernephroma, but, on analysis, observed that the majority of such patients are in the sixth decade or beyond.

Hines and Sander[23] compared the blood pressure on the original examination with the subsequent development of hypertension (160/100 or more) ten and twenty years later in a series of urologic patients and in a control group. They reported a striking coincidence of data in the two series. When the age factor was considered, no significant difference could be found in the incidence of subsequent hypertension. They concluded that the latter is more closely related to the height of the blood pressure on the original examination than to the extent of the renal lesion or the known duration of the urologic disease, and that their data seem to cast doubt on the importance of renal disease in producing hypertension.

Because of the supposed relationship between urologic disease and hypertension, nephrectomy has been recommended by some workers for the relief of elevated blood pressure of patients with unilateral renal lesions. Has it been demonstrated that the removal of the affected kidney in such cases is followed by a reduction in blood pressure? If temporary decreases in the arterial pressure have been observed, has cognizance been taken of the fact that any surgical procedure or even prolonged bed rest without surgical intervention may cause a reduction in blood pressure? Sensenbach[24] recently reviewed the literature on nephrectomy in the treatment of hypertension, and found that, in the 75 cases he collected, only 6.6 per cent of the patients had normal blood pressure two years or more after operation; about one-third had a fall in blood pressure, but had been followed less than two years at the time their cases were reported; one-third showed a reduction, but remained hypertensive, and, in one-third, the blood pressure was unaltered or higher. On the other hand, the observations of Goldblatt[25] and Braasch,[26] in several cases followed over a period of years, seem to offer strong evidence that a causative relationship does occasionally exist. That such relationship must indeed be uncommon is suggested by our failure to establish a correlation between urologic disease and hypertension in this study.

SUMMARY

1. A review of the literature has demonstrated that there is no conclusive proof that urologic disease frequently causes hypertension.

2. Criticisms of methods employed by some investigators in the study of this problem include lack of control series, omission of statistical evaluation of the results, and the use of systolic blood pressure alone in defining "hypertension."

3. Our observations on 357 urologic cases and 654 control subjects tend to invalidate the impression that surgical conditions of the urinary tract as a general group are causally related to elevation of the blood pressure, although the causal relationship in individual cases cannot be denied.

The authors wish to acknowledge their appreciation to Dr. Charles Ferguson for use of urologic case records.

REFERENCES

1. Goldblatt, Harry, Kahn, Joseph R., and Lewis, Harvey A.: Experimental Hypertension, J. A. M. A. **119:** 1192, 1942.
2. Fishberg, A.M.: Hypertension and Nephritis, Ed. 4, Philadelphia, 1939, Lea and Febiger.
3. Calder, Royall, M.: Letter to Editor, J. A. M. A. **120:** 309, 1942.
4. Weiss, S., and Parker, F., Jr.: Pyelonephritis: Relation to Vascular Lesions and to Arterial Hypertension, Medicine **18:** 221, 1939.
5. Barney, J. D., and Suby, H. I.: Unilateral Renal Disease With Arterial Hypertension, New England J. Med. **220:** 744, 1939.
6. Crabtree, E., Chaset, Granville, and Chaset, Nathan: Vascular Nephritis and Hypertension, J. A. M. A. **115:** 1842, 1940.
7. Abeshouse, Benjamin: Hypertension and Unilateral Renal Disease, Surgery **9:** 942, 1942; **10:** 147, 1941.
8. Morlock, C. G., and Horton, B. T.: Variations in Systolic Blood Pressure in Renal Tumor: A Study of 491 Cases, Am. J. M. Sc. **191:** 647, 1936.
9. Braasch, William F., and Jacobson, C. E.: Chronic Bilateral Pyelonephritis and Hypertension, Proc. Staff Meet., Mayo Clin. **15:** 481, 1940.
10. Shure, Norman M.: Pyelonephritis and Hypertension: A Study of Their Relation in 11,898 Necropsies, Arch. Int. Med. **70:** 284, 1942.
11. Braasch, William F., Walters, Waltman, and Hammer, Howard J.: Hypertension and the Surgical Kidney, J. A. M. A. **115:** 1837, 1940.
12. Braasch, William F., and Wood, William W.: Clinical Perinephritis and Its Effect on Blood Pressure, J. Urol. **48:** 343, 1942.
13. Palmer, R. S., Chute, R., Crone, N. L., and Castleman, B.: The Renal Factor in Continued Arterial Hypertension Not Due to Glomerulonephritis, as Revealed by Pyelography. A Study of 212 Cases, With a Report of the Results of Nephrectomy in Nine Cases, New England J. Med. **23:** 165, 1940.
14. Ratliff, Rigon K., and Conger, Kyril B.: The Incidence of Renal Hypertension and of Cure by Nephrectomy, J. Urol. **48:** 136, 1942.
15. Braasch, William F.: Renal Disease as a Factor in Hypertension, Am. J. Surg. **56:** 209, 1942.
16. Schroeder, H. A., and Steele, J. M.: Studies on "Essential Hypertension"; II. The Association of Hypertension With Organic Renal Disease, Arch. Int. Med. **68:** 261, 1941.
17. Williams, J. R., Jr., and Harrison, T. R.: Clinical Pictures Associated With Increased Blood Pressure, A Study of 100 Cases, Ann. Int. Med. **13:** 650, 1939.
18. Wosika, P. H., and Maher, C. C.: The Relationship of Urologic Disease to Types of Hypertension, Urol. & Cutan. Rev. **43:** 815, 1939.
19. Wosika, Paul H., Jung, Frederic T., and Maher, Chauncy C.: Urologic Hypertension as an Entity, AM. HEART J. **24:** 483, 1942.
20. Russek, Henry I.: Blood Pressure in the Aged, AM. HEART J. **26:** 11, 1943.
21. Hines, E. A., Jr.: Range of Normal Blood Pressure and Subsequent Development of Hypertension: Follow-Up Study of 1,522 Patients, J. A. M. A. **115:** 271, 1940.
22. Bicknell, F.: Urological Aspects of Hypertension, J. Michigan M. Soc. **41:** 566, 1942.
23. Hines, E. J., and Sander, H. H.: Factors Contributing to the Development of Hypertension in Patients Suffering From Renal Disease, J. A. M. A. **116:** 1050, 1941.
24. Sensenbach, William: Effects of Unilateral Nephrectomy in Treatment of Hypertension, Arch. Int. Med. **73:** 123, 1944.
25. Goldblatt, H.: Personal communication.
26. Braasch, W. F.: Personal communication.

A MORPHOLOGIC STUDY OF THE CARDIAC CONDUCTION SYSTEM

Part IV: The Anatomy of the Upper Part of the Ventricular Septum in Man

Daniel J. Glomset, M.D., and Richard F. Birge, M.D.
Des Moines, Iowa

THE observers who describe the atrioventricular conduction system of the heart locate its principal parts in the upper part of the ventricular septum and the immediately adjoining right atrial wall. In order to obtain a conception of the anatomy of this region, we have studied, grossly and microscopically, more than forty human hearts. Our observations follow.

The atrial muscles terminate in the atrioventricular fibrous rings. These rings separate the upper and lower cardiac chambers and form the fibrous bases for the atrioventricular valves. The posterior mesial segment of the left atrioventricular fibrous ring swings forward and to the right, terminating in the central fibrous body (trigonum fibrosum) at the level of the posterior aortic wall. The analogous segment of the right ring runs across the upper right ventricular septum, fusing with the septum membranaceum. From the base of the mesial cusp of the tricuspid valve, strong fibrous bands (fila coronaria) extend to the central fibrous body and to the aortic ring in front of it. The central fibrous body, a stout post of connective tissue joining the atrial and ventricular septa, appears to be formed by fusion of the substance of the entire mesial segment of the left ring with a portion of the mesial segment of the right. The anterior portion of the central fibrous body fuses with the aortic ring, which forms the septal base of the aorta and joins the septum membranaceum. The portion of the aortic ring just anterior to the central fibrous body splits into two sheaths, which form a gabled roof for the central part of the muscular ventricular septum. The septal base of the aorta, the septum membranaceum, the fibrous base of the mesial tricuspid, and the endocardium covering the upper part of the septum can be removed by meticulous dissection, which makes plainly discernible the architecture of the upper part of the interventricular septum.

On the left side of the septum, posteriorly, the subendocardial muscle fasciculi radiate toward the central fibrous body where they are attached. Anteriorly, near the upper posterior edge of the septum membranaceum,

Aided by grants from the American Medical Association and the Iowa Methodist Hospital.
Received for publication Feb. 17, 1945.

a similar grouping of superficial fasciculi usually occurs. Near the aortic ring these fasciculi often form a lump from which muscle fibers stream toward the papillary muscles and the apex. Wilhelm His, Jr.,[1] pictures and describes them as the atrioventricular bundle (Fig. 1). We have not observed any muscular connection between these fibers and the ridge fasciculus, the description of which follows. Other careful observers have failed to find, in carnivora, a bifurcation of the fasciculus described by Tawara as the stem of the His bundle. Mahaim depicts the left branch of the His bundle as having four distinct roots originating at separate points of the upper ventricular septum (see Part III).

On the right side of the septum all of the subendocardial muscle fibers behind the fissure, betwen the mesial and anterior cusps of the tricuspid valve, radiate toward the central fibrous body where they are attached (Fig. 2). The most posterior fasciculus runs forward parallel to the ridge of the septum and is attached to the central fibrous body. Similarly, the most anterior fasciculus runs backward; it, also, is attached to the central fibrous body.

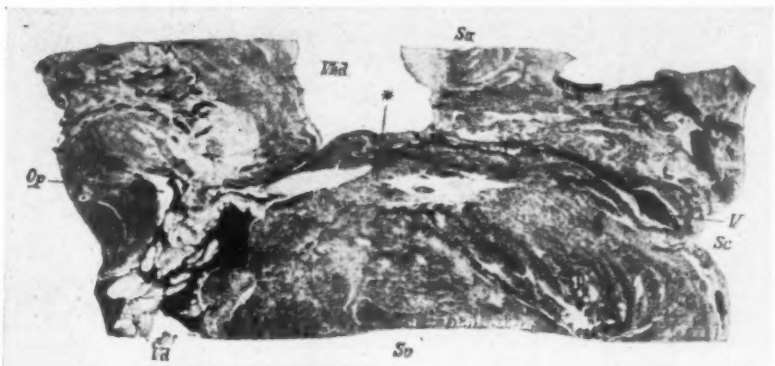


Fig. 1.—Atrioventricular bundle (Wilhelm His, Jr.). Sagittal section of the atrioventricular border of the heart of a newborn human (×7.5). The ventricular septum is cut longitudinally, the auricular septum only partly so. *Vhd*, cavity of the right atrium; *Vd*, cavity of the right ventricle; *Sv*, ventricular septum; *Sa*, atrial septum; *Sc*, coronary groove; *V*, coronary vein; *Op*, pulmonary ostium; and *, atrioventricular bundle.

This most anterior bundle we designate the ridge fasciculus. It has been much studied as the main stem and right branch of the His bundle. This insignificant bundle is not always present. We have found it in over two-thirds of the hearts studied. It, like the rest of the subendocardial muscle fasciculi, varies in size, direction, and relation to other muscle fibers. Its color is, as a rule, lighter than the surrounding, more deeply imbedded, bundles. It originates deep in the ventricular portion of the central fibrous body, from 2 to 3 mm. below the insertion of the atrial muscle fibers (Fig. 2). It runs forward for a short distance in a fibrous canal in the anterior part of the central fibrous body (Fig. 7, Part II) and continues forward and downward toward the right septal papillary muscle. It has a supravalvular and an infravalvular

portion. The supravalvular segment, which is from 1 to 2 cm. long, is slightly oval, and has a diameter of 1 to 2 millimeters. After it emerges from the canal in the central fibrous body, it lies in intimate contact with the other fasciculi of the septum. (Therefore, it seems absurd to believe that the wave of excitation could be insulated in its few muscle cells. We are also unable to understand why this bundle could not be seen with the naked eye.) The infravalvular portion,

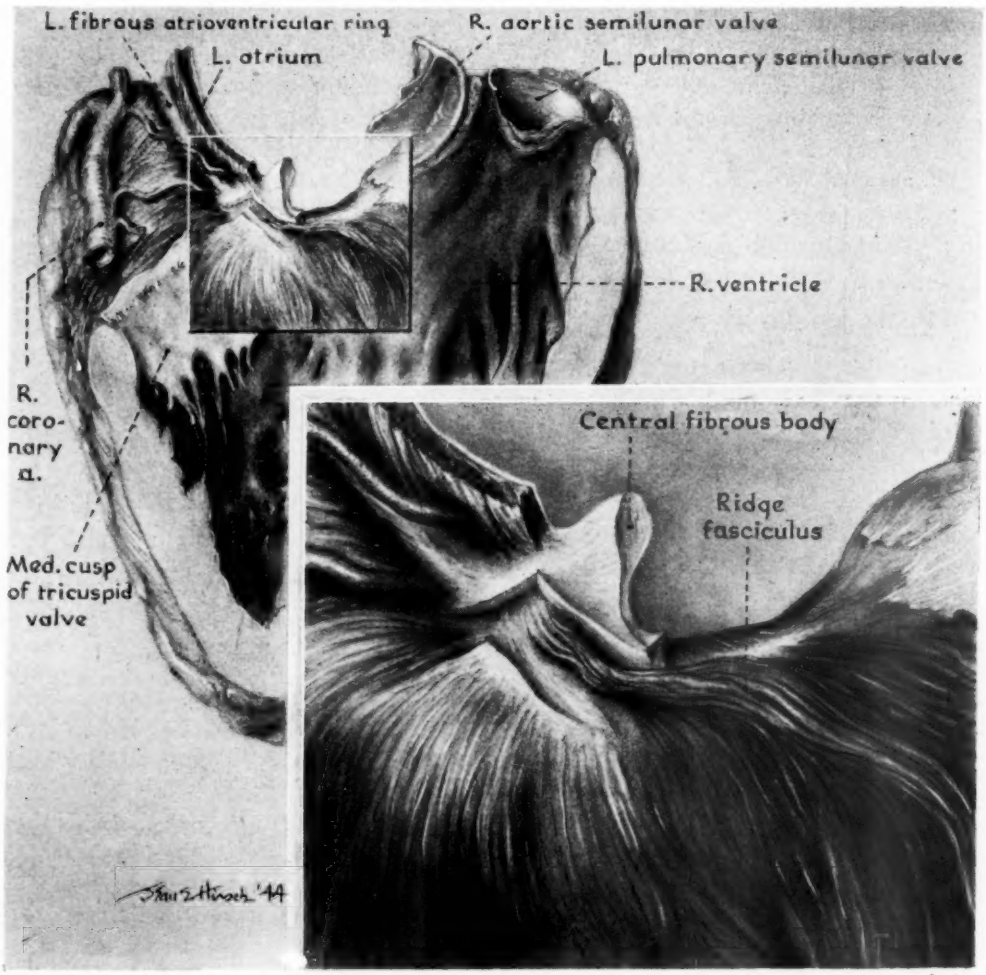


Fig. 2.—A drawing of the ridge fasciculus, showing its origin in the trigonum fibrosum and its relation to the septal musculature, also the ramus septi fibrosi ("artery to the node").

which is often cylindrical, measures about 1 mm. in diameter. It does not possess a special connective tissue sheath. If there is a groove running from the valvular incisure toward the apex, the infravalvular part of the fasciculus lies on the posterior margin of that groove and is often superficial. In hearts in which it is superficial it can be readily fol-

lowed to the base of the papillary muscle. When it lies deeper, it can also be followed. In both cases it can be followed in serial sections.

The histologic structure of the ridge fasciculus, evident in Figs. 3 and 4, is also clearly depicted in Mahaim's microphotographs. We have stated previously that the structure of the fasciculus is identical with neighboring muscle bundles and that we have not encountered blood vessels larger than arterioles in the fasciculus. Nerve fibrils were not detected by the histologic technique which we employed.

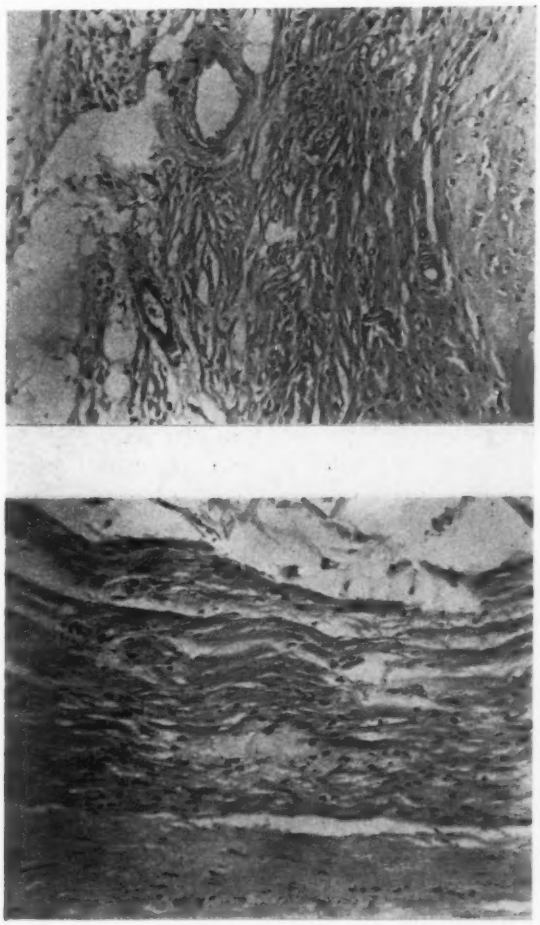


Fig. 3.—Microscopic structure of the supravalvular part of the ridge fasciculus. Longitudinal sections (×75). *A*, "Nodal" region. *B*, "Stem" region.

According to the orthodox view, this ridge fasciculus originates in the atrioventricular node, located in the posterior atrial wall, but in none of the hearts that we studied did we find it entering atrial myocardium. The atrioventricular node is described by Tawara as a reticulum of slender, indistinctly striated muscle fibers from which the His bundle originates. The interstices of the nodal reticulum are filled

with connective tissue, poor in cells. Through the node, or to the side of it, runs the "artery to the node." We have not found such a node in the posterior *atrial* wall in any of the mammals that we have examined. The ramus septi fibrosi (Haas) runs in the atrioventricular groove, and, so far as our observations go, never in the atrial wall. We[2] have described the node of Tawara in ungulates. In these animals it is a part of the musculature of the upper ventricular septum. From it the muscular part of the "Purkinje" bundle arises. The node lies behind the central fibrous body. Its muscle cells change abruptly to the characteristic Purkinje fibers at the place where the nerve trunks enter the bundle.

It has already been stated that in human hearts the ridge fasciculus originates deep in the ventricular part of the central fibrous body. In order to study the origin and the environs of this fasciculus histologically, we removed the posterior atrial wall by severing the central fibrous body below the attachment of the atrial muscle fibers. Blocks were cut from this part of the upper ventricular septum. Posteriorly, the blocks terminated a few millimeters behind the "nodal artery" where it enters the septum; anteriorly, they extended several millimeters in front of the canal in the central fibrous body. Microscopic sections parallel to the muscle fibers of the ridge fasciculus were cut to include the beginning of the fasciculus, in front, and the "artery to the node," behind. The histologic structure of the origin of the ridge fasciculus is shown in Fig. 3, *A*. It is obvious that the appearance of a reticulum in this region is due to the intertwining of ventricular muscle fibers at their attachment to the central fibrous body, and that the muscle fibers are a part of the ventricular septum.

Tandler,[3] Spalteholz,[4] Gross,[5] Mahaim,[6] and, more recently, Lascano[7] have described a special arterial supply to the His-Tawara system in man. On the basis of the theory that the arteries which supply the system are "end arteries," the lesions that are thought to cause block have been assumed to be due to obstruction of the arterial twigs which supply the system. The artery to the node (ramus septi fibrosi, Haas) is said to supply the node and the stem of the His bundle. Gross describes a rather large septal branch of the anterior ramus descendens as the ramus limbi dextri. Mahaim states that the left branch has a double blood supply, that the anterior limb is supplied by a branch from the anterior descending artery and the posterior limb by a branch from the posterior descending artery. The coronary arteries, which supply the septum, have been made visible by means of opaque media by Spalteholz, Gross, and Lascano. The Argentine investigator states: "The arteries entrusted with the blood supply to the node, the bundle of His and its branches, anastomose with one another and do so with the nutrient arteries of the non-specific myocardium—therefore, . . . these arteries are merely the main arteries, not terminal vessels, to the above-named node, bundle, and its branches."

In a special study of the septal coronary arteries of ten human hearts, we made the following observations:

The posterior septal part of the atrioventricular groove is deep (2 to 3 cm. in normal hearts). It terminates anteriorly in the central fibrous body and the aortic ring. The "artery to the node," which runs in this groove, is one of several septal twigs of the coronary artery which gives off the posterior descending branch. In some hearts this

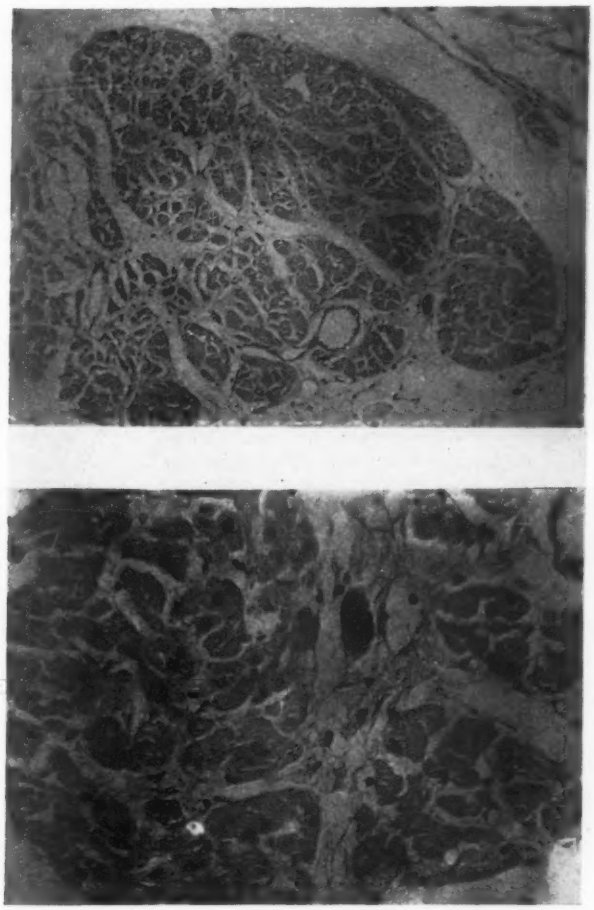


Fig. 4.—Microscopic structure of the infravalvular part of the ridge fasciculus. Cross section. The ridge fasciculus is seen at the extreme right. *A*, Showing relation to other myocardial fibers. *B*, Higher magnification of *A*.

twig does not reach the central fibrous body, but enters the septum some distance behind it (Fig. 2). The diameter of the vessel varies from 1 to 2 millimeters. It lies in the loose, adipose tissue which fills the groove and, as a rule, divides into two or more branches which enter the septal musculature near the central fibrous body. The artery which Gross named "the artery to the right branch of the His bundle"

is the largest septal branch given off from the anterior ramus descendens. It often measures 2 mm. in diameter. It plunges directly into the muscular septum and, by ordinary dissection, can be followed for only a short distance. We are not certain which of the many small branches given off from the anterior and posterior rami descendens are the ones which Mahaim considers the arteries to the anterior and posterior limbs of the left branch of the His bundle.

The observers who describe a special blood supply for the atrioventricular bundle offer no evidence that the arterial twigs which they describe actually supply the "conducting bundle," or that they supply *only* that fasciculus. Their illustrations shed no light on the problem. It seems absurd to us to claim that such *large* arteries have the sole function of supplying the *tiny* ridge fasciculus. As previously stated, no arteries larger than arterioles have been found by us or others in microscopic sections of this bundle. We hold that the special-blood-supply theory is as much a myth as is the concept of the conducting bundle itself.

In the mammalian hearts that we examined we found no valid anatomic evidence to support the myogenic theory of cardiac conduction. It seemed natural, therefore, to search for morphologic evidence for the neurogenic concept. This theory assumes that the cardiac impulse originates in the bodies of motor neurons and is transmitted to the myocardial elements through their axis cylinders. Obviously the activating neurons must be located within the cor itself, because hearts of the most highly developed mammals are capable of rhythmic contraction after all nerve connections with the rest of the body are severed. It is anatomically impossible for a single cardiac chamber to function independently, for the muscle bands which constitute the atrial myocardium run continuously from one atrium to the other, and all the spiral muscles of the ventricles, with one exception, are common to the lower chambers. Clinical and experimental observations clearly indicate that the paired ventricles and paired atria are capable of independent rhythmic contraction. Therefore, if the neurogenic theory is correct, there must exist in the heart at least one atrial and one ventricular pacemaker. Since it has been established that in adult animals cardiac contraction begins in or near the sulcus terminalis, it is logical to search for a nerve pacemaker in this region; and because there is good electrocardiographic evidence that ventricular activation begins in the upper part of the interventricular septum, a ventricular pacemaker may be found in this locality. These theoretic considerations lead to a discussion of the anatomy and physiology of the intrinsic nerve tissue of the heart.

The nerve tissue of the heart has been studied by many investigators. We have reviewed the observations of the following more recent students of this phase of cardiac anatomy: Dogiel,[8] 1899; Müller,[9] 1924; Perman,[10] 1924; Fakutake,[11] 1925; and Woollard,[12] 1926. Their observations are summarized briefly in the following paragraphs.

The ganglia of Remak, Bidders, and Ludwig are but a small part of the extensive nerve tissue found in the hearts of higher animals. The intrinsic nerve elements of the heart consist of nerve cells, nerve trunks, and plexuses of nerve fibrils. The nerve cells occur underneath the pericardium. They are exceedingly numerous in the atria, and are also numerous in the atrioventricular sulcus, but are rarely present in the ventricles. However, Dogiel found ganglion cells in the frog even at the apex, and Woollard found nerve cells in the interventricular furrow of the snake. In man, nerve cells are either scarce or absent in the ventricles. The cells are of four types: (1) The most common type is round or polygonal, sends out from three to ten dendrites, and gives off nonmedullated axis cylinders, some of which have been traced to muscle fibers. (2) A less common type, often found in nerve trunks, is round and has long dendrites and medullated axis cylinders, some of which may terminate in cardiac muscle (Woollard). (3) An uncommon variant of the first two types possesses dendrites which interlace with adjacent cells. (4) A rare type, rosette-shaped, has nonmedullated axis cylinders which appear to end in muscle fibers.

The cells of all types are found singly and in groups varying from a few cells, discernible only by aid of the microscope, to large ganglia readily seen with the naked eye. The ganglia are scattered diffusely under the pericardium of the atria and in the atrioventricular sulcus. The larger chains of ganglia are frequently found around the roots of the vessels. Large collections of nerve cells occur in the atrial wall of the posterior and anterior segments of the ventricular groove in man and other mammals. Anteriorly, these collections are most conspicuous between the root of the aorta and that of the pulmonary artery. In the lateral segments of the atrioventricular groove the nerve cells are few, and occur singly or in tiny groups. Nerve cells located within the nerve bundles are most numerous in the anterior part of the atrioventricular groove.

The nerve trunks, composed of medullated and nonmedullated fibers, extend from the atria to the ventricles in the region of the septum, both anteriorly and posteriorly (Woollard). In the atrioventricular groove and in the ventricles the nerve trunks from which the subendocardial and subpericardial plexuses of fibrils are found follow the coronary arteries. Woollard described fibrils which penetrate the muscle cells, and stated that the nerve fibrils which terminate in nonmuscular tissue have a sensory function.

Wilson[13] first gave an accurate description of the abundant nerve tissue which is present in the Purkinje bundle of the ungulates. All of the observers who have studied the regions of the sinoauricular and the atrioventricular nodes noted nerve cells in close proximity to the "nodes" and found nerve fibrils among their muscle elements. Recently, Nonidez[14] published an illustration showing numerous nerve fibrils lying among the muscle fibers in the His bundle of the dog. In our studies

of the so-called cardiac conduction system, we were astonished at the abundance of nerve cells encountered. The nerve cells seemed more numerous in the right atrium than in the left.

In the sulcus terminalis two types of ganglia were found. The larger groups, consisting of large cells, were closely associated with the entering vagi; the smaller, made up of smaller cells, were found some distance from the nerves. These two types of nerve cells were found in every species examined. Nerve cells were numerous around the inferior vena

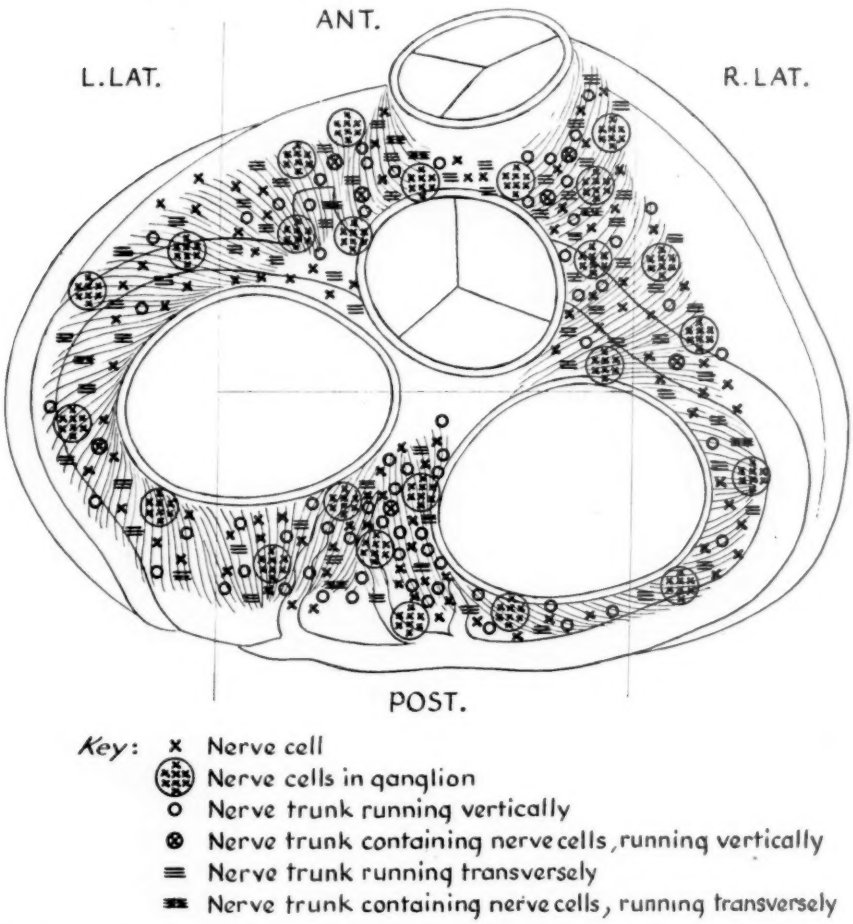


Fig. 5.—A schematic drawing showing the distribution of nerve cells in the atrioventricular groove.

cava. In the horse, we encountered a large collection of nerve cells in the anterior wall of the right atrium, slightly to the left of the opening of the inferior vena cava. In all the ungulates studied, large collections of nerve cells occurred just behind the central fibrous body, and the nerve fibers from these cells constituted more than half of the substance of the Purkinje bundle. Nerve cells were also found in the right and the left branches of this bundle.

In order to obtain more information about the relation of the intrinsic nerve tissue to the upper part of the ventricles, we made longitudinal microscopic sections of three human, and one canine heart in the region of the auriculoventricular sulcus. The blocks were cut to include both the atrial and the ventricular portions of the groove. The material was fixed in formalin, and sections were cut from both ends and the middle of each block. All sections were stained with iron hematoxylin because by this method the nerve cells and nerve trunks are readily

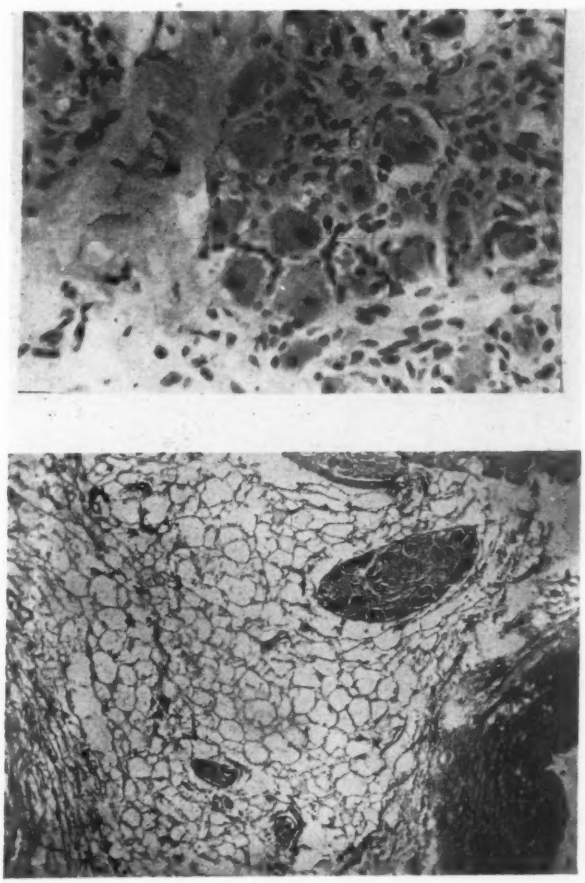


Fig. 6.—Nerve cells in the atrioventricular groove. *A*, Ganglion in loose fatty tissue. *B*, Ganglion in a nerve trunk.

recognized. No attempt was made to study the finer ramifications of the nerve fibers because such studies have already been made by several competent investigators whose observations are essentially in agreement. The heart of a dog was included in this study because we wished to compare the observations in man with those in the dog, and because immediate fixation of the dog heart after death eliminated possible errors due to post-mortem change. The richness of the nerve tissue in

the region studied surprised us. Our observations are shown diagrammatically in Fig. 5; however, from our diagram one does not obtain a correct concept of the large number of nerve cells present. All sections contained nerve bundles and nerve fibers; more than two-thirds of them contained from one to fifty nerve cells. The cells were most numerous in the posterior and anterior septal segments of the atrioventricular groove, but were also found elsewhere in the sulcus. In the groove they occurred singly or in small groups, lying loose in the fatty tissue or inside of the nerve trunks. Ganglia appeared most numerous on the anterior and posterior surfaces of the atria (Fig. 6). Large collections extended from the very surface of the heart to the central fibrous body in the posterior part of the groove. Here they were more numerous on the atrial side, and appeared to have no immediate relation to nerve bundles. The only segment free from ganglion cells was the one which extended from the central fibrous body forward the length of the septal aortic ring. In front of this segment, between the aorta and the pulmonary artery, large collections of nerve cells were found in all hearts.

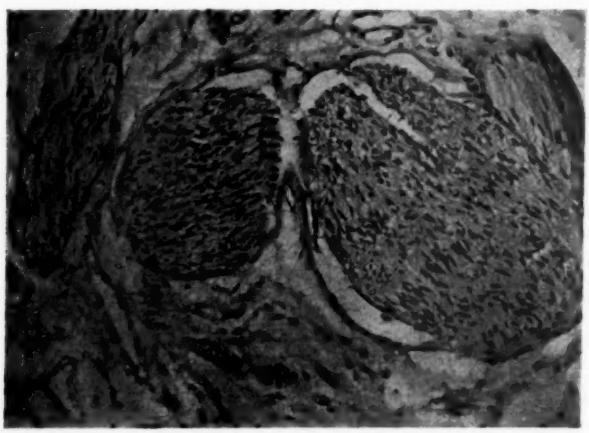


Fig. 7.—Nerve trunks in the atrioventricular groove.

Here they formed an almost continuous mass, extending between the two coronary arteries and lying on top of the anterior portion of the septum. It appears, as Woollard has reported, that the ganglion cells found in the groove on its lateral aspects are extensions of the masses found in the anterior and posterior part of the groove. The posterior mass of ganglia is a direct extension of the nerve tissue between the two atria and around the large veins. The abundance of nerve trunks found in this part of the heart is impressive (Fig. 7). Those found in cross section in the neighborhood of the coronary arteries are undoubtedly nerves following the vessels. In the nerve trunks, in the anterior part of the groove, nerve cells frequently occur (Fig. 6, *B*). Some of the trunks, which were cut longitudinally, probably extend into the ventricles. The nerves in the

ventricles are always found in the neighborhood of coronary vessels. We have found individual ganglion cells in the conus arteriosus, but nowhere else in the ventricles of carnivorous animals. Our study, however, has not been exhaustive.

In mammals an abundance of nerve tissue was found. This tissue consists of nerve cells, apparently limited to the pericardium of the atria and the atrioventricular sulcus; nerve trunks, passing from the atria to the ventricles; and pericardial and subendocardial plexuses of fine nerve fibrils in both the atria and the ventricles. The fibrils of these plexuses lie on the individual muscle fibers, and penetrate some of them (Woollard).

What is the function of these intrinsic nerves of the heart? Obviously, our study does not answer the question. Gaskell[15] held that the cardiac impulse has a nervous origin in the frog, and Carlson[16] showed that the intrinsic nerves of the heart originate and control cardiac contraction in the king crab. We have found ample morphologic support for the neurogenic theory in the hearts that we have examined.

CONCLUSIONS

1. The ridge fasciculus (the His bundle) is a slender muscle bundle in the upper part of the interventricular septum, measuring from 1 to 2 mm. in diameter. It originates in the ventricular portion of the central fibrous body (trigonum fibrosum), runs forward just underneath the mesial part of the aortic fibrous ring, continues caudally underneath the fibrous ring of the tricuspid valve in the fissure between the mesial and the anterior cusps, and extends downward toward the base of the septal papillary muscle. It does not bifurcate, and, therefore, has no left branch. It is not surrounded by a special connective tissue covering, but lies in intimate contact with other muscular elements of the septum from the place where it emerges from the canal in the central fibrous body to the base of the papillary muscle. In some hearts it is covered with muscle bundles which run obliquely across it. It is structurally identical with the other muscle fasciculi of the heart.

2. The ridge fasciculus has no special vascular supply. The ramus septi fibrosi (Haas), a branch of the coronary artery which supplies the ramus descendens posterior, enters the ventricular septum just behind the central fibrous body and probably supplies the arterial blood for the ridge fasciculus. It is possible that the ramus limbi dextri (Gross) may supply the lower part of the fasciculus.

3. We have not found any muscle connection between the fibers of the ridge fasciculus and those of the right atrium.

4. We have found no anatomic evidence to support the myogenic theory of cardiac conduction.

5. The heart has a well-developed, intrinsic nervous system consisting of nerve cells, nerve trunks, and networks of nerve fibrils. The nerve cells are found underneath the pericardium of the atria, and extend

as large and small collections and as individual cells into the atrioventricular groove. These nerve cells are most numerous in the posterior and anterior part of the groove. Most of the ganglia lie near the pericardium. Many collections of cells occur inside the atrioventricular nerve trunks in the anterior portion of the sulcus. Numerous nerve trunks follow the coronary arteries; other nerves extend from the atria to the ventricles posteriorly. Smaller branches sometimes follow the coronary arteries in the ventricles. Woollard and others have shown that the nerve trunks break up into pericardial and endocardial nerve plexuses, both in the atria and in the ventricles.

6. We, therefore, believe that the cardiac musculature is under a nervous control similar to that of other muscle tissue, and consider it physiologically unsound to draw conclusions concerning cardiac conduction without taking cognizance of the rich, intrinsic nerve system of the heart.

REFERENCES

1. His, W., Jr.: Die Thaetigkeit des embryonalen Herzens und deren Bedeutung fuer die Lehre von der Herzbewegung beim Erwachsenen, Arb. a. d. med. Klin. zu Leipz. 14, 1893.
2. Glomset, D. J., and Glomset, A. T. A.: A Morphologic Study of the Cardiac Conduction System in Ungulates, Dog, and Man. Part II: The Purkinje System, Am. Heart J. **20**: 677, 1940.
3. Tandler, J.: Anatomie des Herzens, Jena, 1913, Gustav Fischer.
4. Spalteholz, W.: Die Arterien der Herzwand, Leipzig, 1924, S. Hirzel.
5. Gross, L.: The Blood Supply to the Heart, New York, 1921, Paul B. Hoeber, Inc.
6. Mahaim, I.: Les Maladies Organiques du Faisceau de His-Tawara, Paris, 1931, Masson & Cie.
7. Lascano, E. F.: Irrigación normal del nódulo de Tawara, haz de His y sus ramas, Rev. argent. de cardiol. **10**: 23, 1943.
8. Dogiel, A. S.: Zur Frage ueber den feineren Bau der Herzganglien des Menschen und der Saeugethiere, Arch. f. mikr. Anat. **53**: 237, 1898.
9. Müller, L. R.: Die Lebensnerven, ihr Aufbau, ihre Leistungen, ihre Erkrankungen, ed. 2, Berlin, 1924, Julius Springer.
10. Perman, E.: Anatomische Untersuchungen ueber die Herznerven bei den hoeheren Saeugetieren und beim Menschen, Ztschr. f. d. ges. Anat. 1 Abt., Muenchen u. Berl. **71**: 382, 1924.
11. Fakutake, K.: Beitraege zur Histologie und Entwicklungsgeschichte des Herznervensystems, Ztschr. f. d. ges. Anat. 1 Abt., Muenchen u. Berl. **76**: 592, 1925.
12. Woollard, H. H.: The Innervation of the Heart, J. Anat. Lond. **60**: 345, 1925.
13. Wilson, J. G.: The Nerves of the Atrioventricular Bundle, Proc. Roy. Soc., London, s. B **81**: 151, 1909.
14. Nonidez, J. F.: The Structure and Innervation of the Conductive System of the Heart of the Dog and Rhesus Monkey as Seen With a Silver Impregnation Technique, Am. Heart J. **26**: 577, 1943.
15. Gaskell, W. H.: On the Rhythm of the Heart of the Frog, and on the Nature of the Action of the Vagus Nerve, Phil. Tr., Lond. **173**: 993, 1883.
16. Carlson, A. J.: Vergleichende Physiologie der Herznerven und der Herzganglien bei den Wirbellosen, Ergebn. d. Physiol. **8**: 371, 1909.

Clinical Reports

EMBOLIC THROMBOSIS OF THE ABDOMINAL AORTA WITH TUBERCULOUS (HISTOLOGIC) LESIONS OF THE HEART CONTAINING GIANT CELLS WITH RADIAL INCLUSIONS

ROBERT A. BEEBE, M.D., AND GEORGE H. COLEMAN, M.D.
CHICAGO, ILL.

AMONG the numerous published reports of tuberculous myocarditis and endocarditis there seems to be no record of a complicating mural thrombosis with embolism and thrombosis of the aorta and both common iliac arteries. This sequence of myocardial disease and complication is described in our report. The lesions in the myocardium have additional interest because some of the giant cells in the granulation tissues had radial inclusions. The association of giant cells with radial inclusions in granulomatous lesions of the myocardium resembles the conditions recorded by Diss[1] in the heart muscle of a woman, aged 64 years, with chronic tuberculosis of the lungs. The nodules he described in the myocardium consisted of epithelioid cells and giant cells, and several of the giant cells had asteroid inclusions. No acid-fast bacilli were found in the lesions. A review of the reports of giant cells with radial inclusions, additional descriptions, and an interpretation of the nature of the inclusions was published by Hirsch.[2]

Tuberculous myocarditis is not rare, and in some of the myocardial lesions acid-fast bacilli have been found. Townsend,[3] of Dublin (1832), is considered by some to be the first to describe tuberculous myocarditis. Horn and Saphir,[4] however, stated that Morgagni, in 1761, is generally regarded as the first to have recognized tuberculosis of the heart muscle. From 1832 to 1865 only a few reports were published. In 1865, Haberling, according to Anders,[5] collected twelve cases, some of which were of tuberculous pericarditis only. Sanger, Anders[5] stated, reported twenty-two cases, including three of his own. Anders' review,[5] in 1902, brought the total number reported at that time to seventy-two. Horn and Saphir[4] stated that Raviart had collected one hundred eighty-five cases of tuberculosis of the heart muscle in a review of the literature up to 1906. Of these one hundred eighty-five cases, Raviart considered one hundred twenty-one to be authentic. Saphir,[6]

From the Henry Baird Favill Laboratory of St. Luke's Hospital, Chicago, Illinois.
Aided by the Winfield Peck Memorial Fund.
Received for publication Nov. 17, 1943.

in a general review of myocarditis, mentioned that in only three of the reports included in his review were tubercle (acid-fast) bacilli demonstrated.

Giant cells with radial inclusions have been reported only once in the myocardium. These inclusions of giant cells were described first by Goldman[7] in a dermoid cyst of the neck and, since then, have been observed in various viscera. From observations and experiments, Hirsch[2] concluded that the inclusions probably are a crystalline form of fat, such as palmitin or stearin, which had separated in the lesions from a liquid fat system containing cholesterol or substances with the physical properties of cholesterol, and that gradually, in the tissues, these crystals had become insoluble in the usual solvents for lipids.

CASE REPORT

A white woman, aged 65 years, entered St. Luke's Hospital Nov. 12, 1942, and died Dec. 3, 1942. In August, 1941, the patient had bundle branch block, but she was not decompensated. In August, 1942, in another hospital, a radical, right-sided mastectomy and axillary dissection had been performed. She had symptoms of coronary occlusion on the fifth hospital day. An electrocardiogram at that time revealed slight change from one made the previous year. She entered St. Luke's Hospital because of nausea and vomiting, sweating, salivation, and extreme weakness that began suddenly two hours before admission. The erythrocyte count was 4,620,000, the hemoglobin was 13.6 Gm., and the leucocyte count was 7,350. The urine contained more than 50 mg. per cent of albumin. An electrocardiogram showed partial A-V heart block and intraventricular block. The temperature was 98.4° F.; the pulse rate, 96; the respiratory rate, 28; and the blood pressure, 125/85. There were decreased breath sounds and dullness over the left side of the chest. The heart was grossly enlarged. The tones were irregular and of poor quality, with extrasystoles and gallop rhythm. Roentgenologic examination revealed compression of the lower lobe of the left lung, apparently caused by the enlargement of the heart. The transverse diameter of the heart was increased. Oxygen, aminophylline, digitalis, and sedatives were given as necessary. She was dyspneic, and her condition did not improve. On the tenth day in the hospital numbness in the right foot was noted, and examination showed that this extremity was colder than the left, was anesthetic to the ankle, and was cyanotic. This condition became worse. In the twentieth day in the hospital the left foot showed similar changes. The patient's temperature rose on the eighteenth day to 103.2° F., and the pulse rate increased to 100 per minute and to 160 terminally. She died on the twenty-first day in the hospital.

The essentials of the post-mortem examination (by Edwin F. Hirsch) of the trunk are as follows. The left lung was displaced by the markedly enlarged heart. The pericardial fluid was clear, yellow, and not increased in amount. The lining of the pericardium and epicardium was smooth. The heart weighed 385 grams. The diagonal measurement from the right auricle to the apex was 17.2 cm., and that across the base of the heart was 12.5 centimeters. The thickness of the myocardium of the right ventricle near the septum in front was 2 millimeters. The

pulmonic leaflets were smooth; the tricuspid leaflets had slight fibrous thickenings. The lining of the right auricle and the right auricular appendage was smooth. In the right ventricle, on the septal surface, there were fibrous plaques ranging to 1.1 cm. in diameter, and the lateral wall was rough and granular. The myocardium of the right ventricle, on surfaces made by cutting, was extensively replaced by fibrous tissue. The thickness of the lateral wall of the left ventricle along the septum behind was 0.9 cm. at the apex, and 1.5 cm. at the mitral ring level. There were slight fibrous thickenings of the mitral leaflets, especially of the anterior one. The lining of the left auricle and the left auricular appendage was smooth. Adherent to the lining of the lateral wall of the left ventricle behind the papillary muscles there were several partially organized mural thrombi; the largest was about 2.8 by 1.8 by 0.7 centimeter. Surfaces made by cutting the lateral wall of the left ventricle showed gray-red fibrillar tissue with marked cloudy swelling, and, on surfaces made by cutting the septal myocardium, nearly the entire wall was replaced by scar tissue that extended from 1.3 cm. above the apex to the base, and covered a region 6.3 by 6.8 centimeters.

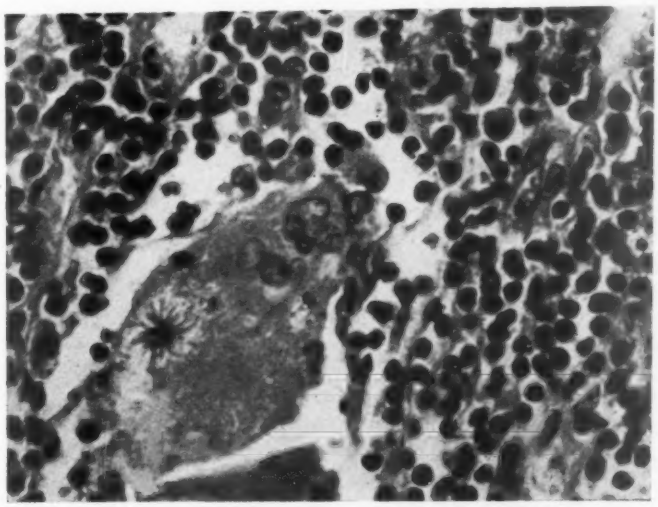


Fig. 1.—Photomicrograph illustrating a giant cell with a radial inclusion (×775).

Three small hyperemic gelatinous regions, about 1 cm. in diameter, were in the center of the scar. The anterior descending branch of the left coronary artery showed fibrous changes, and the lumen was markedly narrowed. There were moderate changes in other portions of the left and the right coronary arteries; the lumina were patent.

In the abdominal aorta, beginning at the upper margin of the celiac axis, there was a firm, ante-mortem, gray-red blood clot which completely filled the lumen and extended into the right and left common iliac arteries, the right and left external and internal iliac arteries, and the right and left femoral arteries. The first portion of the clot contained gray-white fibrinous material. There were recent infarcts in the kidneys, spleen, and the posterior inferior portion of the lower lobe of the left lung. In several of the smaller pulmonary arteries there were obturator thrombi (emboli).

The anatomic diagnosis was: marked chronic fibroplastic myocarditis; mural thrombosis of the endocardium of the left and right ventricles of the heart; cloudy swelling of the myocardium; obturator thrombosis (embolism) of the aorta, the right and left common iliac arteries, the right and left external and internal iliac arteries, and the right and the left femoral arteries; recent infarcts of the kidneys, spleen, and left lung; obturator thrombosis of the smaller branches of the pulmonary arteries; fibrous and fatty changes of the coronary arteries; marked fibrous stenosis of the anterior descending branch of the left coronary artery; chronic fibrous tuberculosis of the lungs; calcification of the tracheobronchial lymph nodes and of the parabronchial lymph nodes; and gangrene of both legs and feet.

Sections of the lateral wall of the left ventricle which included portions of the mural thrombus were examined microscopically. Beneath the narrow epicardium was a wide zone of fat tissue, much of which was necrotic. Most of the myocardium was replaced by hyalinized fibrous scar tissue. Portions also had masses of granulation tissue composed of epithelioid cells, lymphocytes, and scattered multinucleated and vacuolated giant cells. Some of the later giant cells contained refractile radial inclusions (Fig. 1). The adjacent interstitial connective tissue also was infiltrated by granulation tissue. Along the endocardial margin there were granulation tissue thickenings containing lymphocytes, epithelioid cells, and a few Langhans giant cells (Fig. 2). On the endocardium here there were mural thrombi. The main portions of the thrombi were fibrin, with scattered erythrocytes, lymphocytes, and, in some places, polynuclear leucocytes. Sections of the granulation tissue in the myocardium were stained according to the Ziehl-Neelsen method for acid-fast bacilli. Two structures closely simulating acid-fast bacilli were found in these lesions. No acid-fast organisms were found in the endocardial lesions or in the thrombus material.

The dense tissue in the upper lobe of the right lung had a few scattered lymphocytes in a vascular fibroplastic tissue and several blood vessels. Toward the periphery there were diffuse aggregates of lymphocytes, epithelioid cells, and many multinucleated giant cells in a hyalinized fibrous stroma. Many of these giant cells also had large stellate refractile inclusions surrounded by small vacuoles containing refractile granules. A few large mononuclear cells contained particles of carbon. The parabronchial lymph nodes showed similar lesions, containing giant cells with stellate inclusions. The lesions in the kidneys, in the spleen, and in the lung were recent infarcts.

The histologic diagnosis was: chronic fibrous tuberculosis of the myocardium; chronic fibrous tuberculosis (histologic) of the lungs and hilar lymph nodes; recent infarcts of the kidneys, spleen, and lungs; etc.

Mural thrombosis with tuberculous myocarditis is not uncommon. According to Marhsall,[8] cardiac thrombi were described first by Rokitansky, and were studied by Birch-Hirschfeld.[9] Birch-Hirschfeld[9] found, in the right auricle of a man who had genitourinary and pulmonary tuberculosis, an adherent fleshy mass which at first was thought to be a primary sarcoma but microscopically was a tuberculous thrombus composed of leucocytes and organizing caseous thrombus material. Tarozzi[10] noted a nodule over the papillary muscle of the tricuspid valve, about which a thrombus had formed, in the body of a person who had tubercu-

losis. Moser[11] stated that thrombi of the wall sometimes accompany large solitary tubercles, which by far are the commonest form of cardiac tuberculosis. Townsend[3] described a large tuberculous mass almost an inch thick in the wall of the left auricle. Death resulted from asphyxia because the mass compressed the pulmonary veins. Hoisholt, according to Moser, [11] in a case of pulmonary tuberculosis, found a lesion 3.5 cm. in thickness in the wall of the left ventricle of the heart. There was

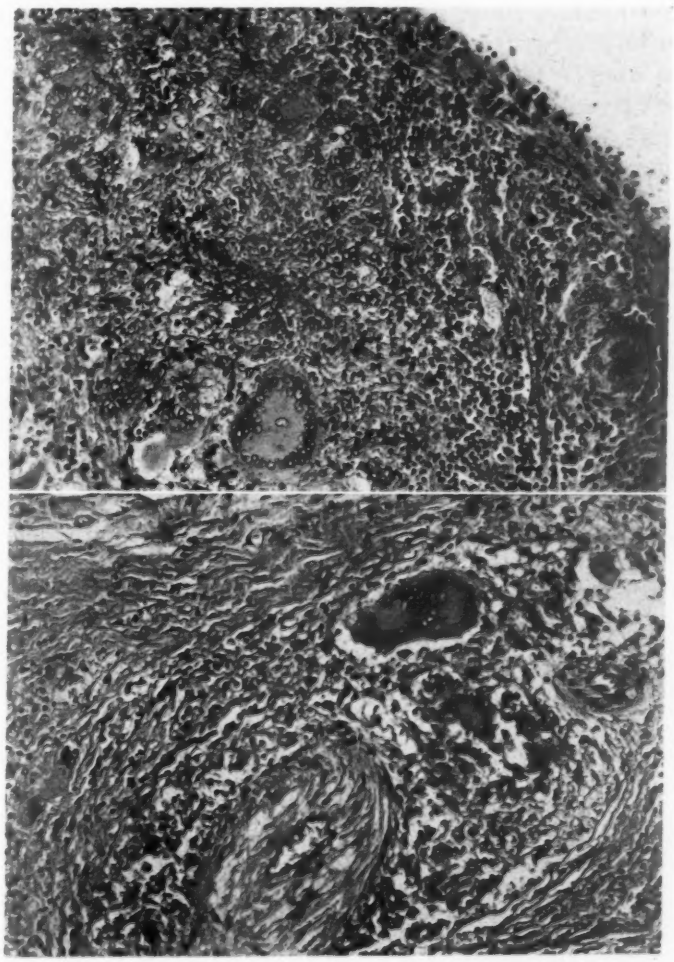


Fig. 2.—*A*, Photomicrograph illustrating an endocardial mass of chronic granulation tissue (×198). *B*, Photomicrograph illustrating a perivascular mass of chronic granulation tissue in the myocardium (×198).

a similar mass in the upper part of the right auricle. Moser[11] observed a firm yellow thrombus at the apex of the left ventricle in a case of tuberculosis of the lungs. Pueschman, according to Anders,[5] described a caseous tubercle which extended through the wall of the right auricle

and was covered by a thrombus containing many tubercle (acid-fast) bacilli. Adamson[12] reported tuberculous tissue which projected into the auricle, although it had not ulcerated the endocardium. Stein and Giering[13] described cardiac thrombi as a complication of mitral stenosis with pulmonary tuberculosis, but tuberculosis of the heart was not mentioned nor was a microscopic report given. Anders[5] stated that it was difficult to say why these tubercules often attained such a size, and yet so rarely ruptured into the blood stream. Others have stated that these thrombi are a potential source of embolic dissemination of infection to other parts of the body, but nowhere was a report of such embolism found. Mural thrombosis of the heart in this patient without much doubt was related to the myocardial lesion. Auricular fibrillation as a cause of thrombosis, accordingly, deserves little consideration. Rheumatic heart disease also is excluded because of the absence of characteristic lesions.

According to Horn and Saphir,[4] the heart may be infected by tuberculosis either by direct extension through the lymphatic channels or by the blood stream. Involvement by direct extension occurs in the large nodular type of pulmonary tuberculosis. Here the right auricle is most often involved because of its proximity to the bronchial nodes. In the lymphatic spread the channels of the bronchial nodes and of the heart and pericardium are closely associated, and, by retrograde flow, the heart and the pericardium may be infected. The blood stream is a source in miliary tuberculosis.

The blood stream seems to be the likely medium for the myocarditis in this report, although others (Horn and Saphir,[4] Anders[5]) have stated that lymphatic spread is by far the most common. The pericardium was not involved grossly. The endocardial lesions resulted from extension from the myocardium, and mural thrombosis developed on the damaged endocardial surface. From this, emboli were released and caused thrombosis of the abdominal aorta, iliac arteries, spleen, kidneys, and left lung.

Stellate inclusions were observed in the lungs with changes which were histologically tuberculous, in the tracheobronchial lymph nodes, in the various hilar lymph nodes, and, in particular, in the myocardial lesions. Diss,[1] as stated, reported giant cells with radial inclusions in the myocardium with pulmonary tuberculosis, but he found no acid-fast organisms in the cardiac lesions. The inclusions in our report were like those described by Hirsch.[2] They varied in size and in the number of spiny projections radiating from a central body. About the periphery of many of the inclusions were small vacuoles.

SUMMARY

Tuberculous myocarditis with endocardial thrombosis is not infrequent, but embolism from these thrombi seem to occur rarely. Tuber-

culous lesions of the myocardium and endocardium, associated with mural thrombosis and obturator thrombosis (embolism) of the abdominal aorta and other vessels, is reported.

Some of the giant cells in the lesions of the myocardium, lymph nodes, and lungs contained radial inclusions.

REFERENCES

1. Diss, A.: Les corps asteroids dans les cellules giantes, Bull. et mem. Soc. anat. de Paris **94**: 349, 1924.
2. Hirsch, E. F.: Radial Inclusions of Giant Cells, Arch. Path. **20**: 665, 1935.
3. Townsend, Rich: Case 5, Dublin J. M. Sc. **1**: 176, 1832.
4. Horn, H., and Saphir, O.: The Involvement of the Myocardium in Tuberculosis, Am. Rev. Tuberc. **32**: 492, 1935.
5. Anders, J. M.: Tuberculosis of the Myocardium, J. A. M. A. **39**: 1081, 1902.
6. Saphir, O.: Myocarditis, Arch. Path. **33**: 88, 1942.
7. Goldman, E. E.: Eine öehaltige dermoid Cyste mit Riesenzellen, Beitr. z. path. Anat. u. z. allg. Path. **7**: 553, 1890.
8. Marshall, H. T.: Endocarditis in Tuberculosis, Bull. Johns Hopkins Hosp. **16**: 303, 1905.
9. Birch-Hirschfeld, Centralbl. f. allg. Path. u. path. Anat. **2**: 807, 1891.
10. Tarozzi, G.: Beitrag zur Kenntnis der Endocarditis tuberculosa. Centralbl. f. allg. Path. u. path. Anat. **14**: 700, 1903.
11. Moser, A.: Tuberculosis of the Heart, Med. and Surg. Rep. of the Boston City Hosp. Series **11**: 194, 1900.
12. Adamson, W. W.: A Case of Tuberculosis of the Myocardium, J. Path. & Bact. **23**: 399, 1919-1920.
13. Stein, S. C., and Giering, J. F.: Cardiac Thrombi Complicating Mitral Stenosis With Pulmonary Tuberculosis in a Man, Pennsylvania M. J. **44**: 183, 1940.

Abstracts and Reviews

Selected Abstracts

Hyman, C: Filtration Across the Vascular Wall as a Function of Several Physical Factors. Am. J. Physiol. **142**: 671, 1944.

A method for determining the filtration rate under controlled conditions is presented. This method depends on the continuous recording of the weight of a perfused preparation. The relationship between the osmotic pressure of the perfusion medium and the filtration rate is established for four colloidal systems: albumin, reconstituted plasma, pectin, and gelatin. The relationship between the perfusion pressure and the filtration rate is established for three types of perfusion medium: colloid-free saline, albumin solutions, and several dilutions of reconstituted plasma. The following conclusions may be drawn from the data presented:

a. There is an inverse linear relationship between the osmotic pressure of the perfusion pressure and the filtration rate when albumin or plasma is used.

b. There is a direct linear relationship between the perfusion pressure and the filtration rate.

c. The blood vessels of the preparation used can retain to a high degree molecules of the magnitude of albumin.

d. The blood vessels of the preparation used probably permit the passage of some fraction of the poly-dispersed gelatin system.

e. The effective osmotic pressure of a colloid in the vascular system is equal to the osmotic pressure determined in a physical osmometer only if the membrane used in the osmometer and the vascular wall both retain the same fraction of the colloidal system.

AUTHOR.

Evans, G.: Clinical Manifestations of Arteriosclerotic Disease. Practitioner **153**: 129, 1944; **Hoskin, T. J.: Diagnosis and Treatment of Coronary Diseases.** Practitioner **153**: 136, 1944; **Wilkinson, K. D.: Diagnosis of Congenital Heart Disease.** Practitioner **153**: 146, 1944; **Cookson, H.: The Treatment of Congestive Heart Failure.** Practitioner **153**: 155, 1944; **Watkins, A. G.: Management of Rheumatic Heart Disease in Early Life.** Practitioner **153**: 161, 1944.

Each of the above articles discusses clinically the subject under consideration. The material is didactic but presents conservative opinion and the presentation is interesting. It should be important reading for those seeking information on each subject. The article on heart disease in early life is particularly important.

MCCULLOCH.

Miller, H.: Spontaneous Mediastinal Emphysema With Pneumothorax Simulating Organic Heart Disease. Am. J. M. Sc. **209**: 211, 1945.

Spontaneous mediastinal emphysema is briefly discussed with a short review of the pertinent clinical and experimental literature. Four new cases of spontaneous mediastinal emphysema associated with left-sided pneumothorax are described in which the clinical history, physical examination, or electrocardiographic examination simulated organic heart disease.

AUTHOR.

Evans, W.: The Unity of Paroxysmal Tachycardia and Auricular Flutter. Brit. Heart J. 6: 221, 1944.

A right pectoral electrocardiogram (CR_4) demonstrated the presence of A-V dissociation, usually 2:1, in twenty-seven consecutive cases of paroxysmal tachycardia. Further investigation is necessary before assigning this feature to all or to the majority of such patients.

In the meantime the finding suggests the common unity of paroxysmal tachycardia and auricular flutter, with auricular tachycardia as the essential mechanism of each, showing variations in rate and in the degree of A-V dissociation.

AUTHOR.

Szekely, P.: Chest Leads for the Demonstration of Auricular Activity. Brit. Heart J. 6: 238, 1944.

Special chest leads were used for the study of auricular activity and compared with the standard leads. The exploring electrode was placed in the third intercostal space at the right sternal border and paired with the right arm or left leg. The former lead was referred to as auricular Lead R; the latter, as auricular Lead F. Auricular Lead F was found to be more useful than auricular Lead R.

These special chest leads were studied in cases with paroxysmal tachycardia, with auricular fibrillation and flutter, and in a number with sinus rhythm. They often showed auricular waves to much better advantage than did the standard leads. It is suggested, therefore, that the recording of these leads is indicated in all cases in which there is doubt about the activity of the auricles.

No correlation was found between the size of the right auricle and the amplitude of the P waves as recorded in the auricular leads. It seems, therefore, that the amplitude of the P wave in the auricular leads is also determined by factors other than the size of the right auricle. The anatomic position of the right auricle in the thoracic cavity and its relation to the anterior chest wall are suggested as possible factors.

AUTHOR.

Tubbs, O. S.: The Effect of Ligation on Infection of the Patent Ductus Arteriosus. Brit. J. Surg. 32: 1, 1944.

The anatomy, physiology, and pathology of the ductus arteriosus are briefly reviewed.

Nine cases of subacute bacterial endarteritis complicating a patent ductus and treated by ligation are described; six of these patients are well today, from fifteen months to over four years after operation.

The technique of the operation is described.

The reason why ligation frequently results in cure of the infection is discussed.

The effect of ligation on infection of a patent ductus has been dramatic, although perhaps unexpected, and infection must now be considered an absolute and urgent indication for operation. Under these circumstances it is important that the supervention of infection should be diagnosed early; any patient with a patent ductus who runs an unexplained fever for more than two weeks should be suspected of this complication.

AUTHOR.

Boone, J. A., and Levine, S. A.: The Development and Interpretation of the Auscultatory Signs of Mitral Stenosis. J. South Carolina M. A. 40: 203, 1944.

During a study of 225 cases of "potential rheumatic heart disease" and "rheumatic mitral insufficiency" followed closely over a period of five to twenty-three years, the auscultatory findings leading up to a final diagnosis of mitral stenosis

in seventeen cases were observed and described. In twelve of these cases the finding of a rumbling apical mid-diastolic murmur preceded by months or years the appearance of the classical presystolic crescendo murmur of mitral stenosis. In ten other cases of the 225, a similar mid-diastolic murmur was subsequently found to disappear. The appearance of accentuation of the apical first heart sound and of the pulmonic second sound in rheumatic patients should stimulate the clinician to search more diligently for definite signs of valvular disease, but of themselves are of little practical help in forecasting the development of mitral stenosis. The presence of apical systolic murmurs of slight intensity and of apical third heart sounds seem to have no practical implications.

The results of the study suggest that in adolescent and young adult rheumatic patients a definite diagnosis of mitral stenosis should be made only on the finding of a long rumbling presystolic apical crescendo murmur ending in an accentuated first heart sound. The diagnosis may be suspected on the finding of definite apical mid-diastolic murmurs, but with the expectation that approximately half of these murmurs will disappear with further observation.

AUTHORS.

Loewe, L.: The Combined Use of Penicillin and Heparin in the Treatment of Subacute Bacterial Endocarditis. Canad. M. A. J. 52: 1, 1945.

Seventh Annual Louis Gross Memorial Lecture delivered at the Jewish General Hospital, Montreal.

Age and sex have no bearing on the outcome of therapy.

The type of organism, apart from the so-called streptococcus species is immaterial to the outcome of therapy, provided it is inhibitable by penicillin, within practical limits, 0.007 to 0.125 Oxford units).

If the patient is in good physical condition, the duration of the disease is less than three months, and the causative organism is sensitive to penicillin, a satisfactory result may be anticipated, barring accidents, in virtually every case.

AUTHOR.

Guy, P. F.: Rheumatic Fever of Childhood. Northwest Med. 43: 166, 1944.

Problems encountered in the diagnosis of one hundred seventy-eight cases of rheumatic fever admitted to the Children's Orthopedic Hospital of Seattle are itemized.

The five manifestations of rheumatic fever are discussed, and the abstract of a case history including all five is given.

The onset of rheumatic fever and the frequency of a preceding episode in the one hundred seventy-eight cases are analyzed and reference is made to the part played by the *Streptococcus hemolyticus.*

The value of continuous institutional care during the toxic period is discussed.

Tonsillectomy in rheumatic fever patients, the age of onset, and other observations are analyzed.

AUTHOR.

Moss, J. E.: Asymptomatic Heart Disease in Young Adults. South. M. J. 37: 63, 1944.

In the examination of a group of supposedly healthy candidates for military service, the incidence of organic heart disease was 0.5 per cent. The incidence of the various etiological types conformed with the generally accepted statistical data.

Despite a number of previous examinations, only 16 per cent of the cases of organic heart disease had been told of their defect, and only 8 per cent considered their hearts abnormal at the time of examination.

By standardization of criteria as to what constitutes a significant abnormality and by more universal adoption of a more complete method of examination, much could be done to eliminate errors of diagnosis.

It is believed that individuals with organic heart disease, even in asymptomatic cases, should be acquainted with the presence and nature of their disease in order that they may properly adjust themselves to a routine of life designed to produce maximum efficiency for the longest period of time.

AUTHOR.

Moses, L. E.: Mechanism of the Effect of Hyperthyroidism on Cardiac Glycogen. Am. J. Physiol. **142:** 686, 1944.

Methods were developed for accurate and consistent determination of heart rate, oxygen consumption, and cardiac glycogen in the white rat. A technique was also devised for the removal of large amounts of blood from the rat's tail. Standard "predictable" levels of heart rate and basal metabolic rate were established in 110 rats. After approximately two weeks of experimental manipulation, cardiac glycogen contents were determined and compared, in relation to the changes produced in heart rate and metabolic rate, with normal controls and with each other. Moderate hyperthyroidism was found to deplete heart glycogen to an extent directly related to the increase in heart rate but not closely related to the metabolic stimulation. Atropine and chilling (by depilation) decreased heart glycogen, in relation to the tachycardia produced, to a degree similar to that obtained in hyperthyroidism. Caffeine caused a smaller loss of heart glycogen, with reference to the stimulation of heart rate, than would have been predicted from the effects of thyroid, atropine, and chilling. This might have resulted from the increased blood pressure and the coronary dilatation characteristic of caffeine medication. Primary anemia produced a decrease in heart glycogen roughly correlated with the decline in hemoglobin content of the blood. Cobalt polycythemia seemed, to a slight extent, to protect the hyperthyroid heart from loss of its glycogen stores. The decrease in heart glycogen of nineteen hyperthyroid rats was participated in by both the left and right ventricles. Loss by the left ventricle was greater by an average of 37 per cent, but the variability of results, due to technical difficulties, renders this difference not statistically as significant as might be desired.

It is concluded that the decrease in heart glycogen by hyperthyroidism is not due to any specific "toxic" influence of the thyroid hormone. The suggestion is tentatively offered that the glycogenolytic action is exerted through a relative ischemia caused directly and indirectly by the increased cardiac activity.

AUTHOR.

Alberti, V. A., Segura, R. G., and Lanari, A.: Mechanisms of Respiratory Variations of Arterial Pressure on the Pulmonary Circulation. Medicina, Buenos Aires **4:** 412, 1944.

The changes in pulmonary and systemic pressure induced by ordinary breathing and artificial breathing are studied without opening the thorax, without opening the thorax but with an exposed heart, and with thorax opened. The Hamilton's hypodermic manometer was used for pressure readings.

With ordinary breathing, pressure falls during inspiration in both the systemic and pulmonary circuits although somewhat delayed (two or three beats) in the former as compared with the latter.

The importance of the diminution of the intrathoracic pressure during inspiration is stressed, as a result of which there is an increase in the capacity of the pulmonary bed with a diminished flow to the left ventricle and a subsequent fall in the systemic pressure.

With artificial respiration the systemic pressure falls during inflation, due to an increase of resistance of the pulmonary circuit. With artificial respiration and high hyperpressure the inflow to both ventricles is hampered in addition to the increased resistance of the pulmonary circuit, which determines the fall of the systemic pressure and the reduced pulse pressure in both circuits.

AUTHORS.

Proskauer, G. G., Neumann, C., and Graef, I.: The Measurement of the Blood Pressure in Rats With Special Reference to the Effect of Changes in Temperature. Am. J. Physiol. **143**: 290, 1945.

The relation between blood pressure, cardiac rate, and the temperature of the rat has been investigated. Indirect (plethysmographic) and direct (Hamilton's optical manometer) methods for measuring the blood pressure were used.

The systolic pressure of trained, normal unanesthetized rats, as measured by a modification of the indirect method in which there is no change in the rectal or cutaneous temperature, was 65 to 95 mm. Hg at room temperature (24° to 28° C.). To avoid the elevation of body temperature that occurs when animals are held in containers with solid walls, an animal holder with walls of wire mesh was found useful.

Elevating the cutaneous and rectal temperatures of normal anesthetized or unanesthetized rats was regularly followed by a progressive rise in blood pressure. The more rapidly the cutaneous temperature was increased, the more rapid was the blood pressure response. Fluctuations in cutaneous temperature corresponded more closely in time and extent with the changes in blood pressure, than did the changes in rectal temperature.

Depressing the temperature of normal unanesthetized or anesthetized rats was followed by a fall of blood pressure; after thirty minutes or more the blood pressure rose again, occasionally to hypertensive levels. Cardiac rate rose and fell with the blood pressure except in heat stroke, when it remained accelerated after the pressor effect had disappeared.

AUTHORS.

Medoff, H. S., and Bongiovanni, A. M.: Age, Sex and Species Variations on Blood Pressure in Normal Rats. Am. J. Physiol. **143**: 297, 1945.

Blood pressures in a series of one hundred and thirty Wistar Albino rats and thirty-three Wistar Gray Norways were determined. The Wistar Albinos exhibit a definite tendency toward higher blood pressures with increasing age. No sex differences in blood pressure were noted in the Wistar Albino rats. There are no significant blood pressure differences between these two species.

AUTHORS.

Dick, G. F.: Experimental Hypertension; Its Production in Dogs by Intravenous Injection of Streptococci. Arch. Path. **39**: 81, 1945.

Hypertensive states comparable to essential hypertension and hypertensive renovascular disease in man have been produced in dogs by intravenous injections of streptococci and other bacteria.

AUTHOR.

Dexter, L. Haynes, F. W., and Bridges, W. C.: The Renal Humoral Pressor Mechanism in Man. I. Preparation and Assay of Human Renin, Human Hypertensinogen, and Hypertensin. J. Clin. Investigation **24**: 62, 1945.

Methods for the preparation of hypertensin and of human renin and hypertensinogen free from hypertensinase have been described, together with their assay by modifications of the methods of Braun-Menendez, Fasciolo, Leloir, Munoz, and Taquini.

AUTHORS.

Lendrum, B., Kondo, B., and Katz, L. N.: The Role of Thebesian Drainage in the Dynamics of Coronary Flow. Am. J. Physiol. **143**: 243, 1945.

The coronary arteries were perfused in dogs' hearts obtained immediately after the animals were sacrificed, and the drainage into the coronary sinus, right auricle, right ventricle, left auricle, and left ventricle were measured. Special umbrella-like partitions were used to seal the A-V openings.

The averages and standard deviation of the percentage flows obtained were: coronary sinus, *36.4 per cent + 11.8 per cent;* the right auricle, *24.5 per cent + 6.5 per cent;* the right ventricle, *30.8 per cent + 5.4 per cent;* the left auricle, *1.4 per cent + 1.7 per cent;* the left ventricle, *7.0 per cent + 3.3 per cent.*

Details of technique and errors of method were discussed.

The flow into the right ventricle via the Thebesian channels was shown to be of significant magnitude.

AUTHORS.

Opdyke, D. F.: The Survival of Dogs Treated With Neosynephrin During the Production of Hemorrhagic Shock. Am. J. Physiol. **142**: 576, 1944.

Twelve dogs were subjected to hemorrhagic shock by controlled bleeding. Neosynephrin was infused during the severely hypotensive period (30 mm.) at a rate which maintained the level of blood pressure between 50 and 75 millimeters. At the end of the infusion period (thirty-four to forty-five minutes) the dogs were reinfused with their own blood, and the subsequent course of events observed. Eight of the dogs died in shock and one recovered from this treatment, while three dogs died of cardiac failure during the infusion of neosynephrin. The average survival time of the dogs dying in shock was 13.4 hours as compared with 5.3 hours in a control series.

It is concluded that any increase in peripheral damage due to an augmented vasoconstriction is compensated for by an increased flow of blood through the vital centers resulting in an increased survival time, but no permanent improvement. However, the use of pressor drugs during severe hypotension seems to be contraindicated because of the direct or indirect damage to the myocardium which may result from their use. The beneficial result of use of pressor drugs in the treatment of shock is questionable from a therapeutic standpoint.

AUTHOR.

Henstell, H. H., and Gunther, L.: Studies of Plasma Volume in the Human Being; Comparative Results of Reduction of Plasma Volume, Intramuscular Pressure and Venous Pressure in Surgical Shock. Am. J. M. Sc. **209**: 187, 1945.

Peripheral circulatory failure in surgical shock may be evident with a normal and unchanged plasma volume. A decrease in plasma volume up to 590 c.c. is not necessarily followed by peripheral circulatory failure. Change in the clinical condition of the patient, for the worse or for the better, and the presence or absence of peripheral circulatory failure, coincide more closely with decline of, or the heightening of, intramuscular pressure, than with changes in the plasma volume. Peripheral circulatory failure may be manifest with a normal or with a decreased plasma volume, but not with an unchanged intramuscular pressure, which remains in the normal range. The circulatory failure is always associated with a lowered level of intramuscular pressure.

An inadequate peripheral circulation, despite a plasma volume decrease of at least 416 c.c., can be compensated and returned to adequacy with the restoration of a low intramuscular pressure to a higher level by the use of nikethamide. Changing increments of intramuscular pressure are an important factor in the dynamics of the peripheral circulation. The kinetics of the peripheral circulation as related to intramuscular pressure (the venopressor mechanism) and other forces that may consti-

tute the venous pump in man, are worthy of greater attention in investigations of the problem of shock; these studies must be made on the human being, preferably, rather than on other animals.

AUTHORS.

Jackson, R. L., Einstein, A. J., Blau, A., and Kelly, H. G.: Angle of Clearance of the Left Ventricle as an Index to Cardiac Size. Modified Technic for Its Determination and Range of Values for Normal Children. Am. J. Dis. Child. **68**: 157, 1944.

A modified technique was established for determining the amount of rotation of the subject necessary to make the left lower border of the cardiac silhouette (left ventricle) clear the projection of the transverse processes of the spinal column (the first angle of clearance) and the left lower border of the cardiac silhouette clear the anterior border of the bodies of the vertebrae (the second angle of clearance) in fluoroscopic examination.

Judging from the data obtained by repeated examination to establish the reliability of the method, not more than 10 per cent of the single measurements vary more than 5 degrees from the true value for the subject. For eleven of the sixteen children for whom repeated measurements were made, the mean deviation from the true value was less than 3.5 degrees for both angles of clearance.

For 102 normal children examined to determine the normal values, the values for the first angle of clearance ranged from 38 to 67 degrees and for the second angle, from 46 to 86 degres. The mean value for the first angle of clearance was 51.8 degrees and for the second angle of clearance, 63.2 degrees. The standard deviations were 5.8 and 7.4 degrees, respectively. Children with vertically placed hearts showed clearance at a smaller angle than children with transversely placed hearts. There are no significant differences in the angle of clearance of the left ventricle in relation to age or sex. Stocky children tend to have greater than average angles of clearance.

It is the belief of the authors that fluoroscopic examination to determine the angles of clearance of the left ventricle is valuable as a supplementary means of studying the heart if the examination can be repeated and the results of subsequent examinations can be compared. Any significant change from the original values could then be interpreted as a change in the size of the heart.

AUTHORS.

Gillesby, W. J.: Cardiac Tamponade. Report of Stab Wound in the Right Ventricle. Mil. Surgeon. **95**: 284, 1944.

A case of stab wound of the right ventricle with penetration of the left pleural cavity is presented in detail. An extensive transpleural approach was used and is advocated as an "all-purpose" incision. Hyperventilation was used to prevent pulmonary complications. The pericardium was left open in communication with the left pleural cavity to permit effusion to drain into the pleural cavity. Electrocardiographic tracings taken postoperatively show only an inversion of the T wave in Lead IV.

AUTHOR.

Irish, U. D., and Jaques, L. B.: Effect of Dicumarol Upon Plasma Fibrinogen. Am. J. Physiol. **143**: 101, 1945.

Plasma fibrinogen was determined in dogs injected with varying amounts of dicumarol. The administration of dicumarol has an effect on plasma fibrinogen as well as on plasma prothrombin. Large doses tend to lower the plasma fibrinogen concentration; smaller doses raise it. These results are similar to those obtained with liver toxins.

AUTHORS.

Thomas, W. C., and Harrison, T. R.: The Effect of Quinidine on the Mortality of Rats With Experimental Myocardial Injury. Am. J. M. Sc. **208**: 756, 1944.

The results obtained from ninety-nine volunteer, hospitalized subjects indicate that the incidence of unfavorable reactions, with the possible exception of vomiting, is not increased by the concomitant administration of sulfathiazole and quinine or atabrine. The highest doses studied were: 6 Gm. of sulfathiazole daily for seven days; 2 Gm. of quinine bisulfate for the same period; and 0.3 Gm. of atabrine daily for five days.

The combination of drugs produced no detectable changes in the amount of hemoglobin or the total white blood count.

Quinine and atabrine produced only minor changes in the free and total sulfathiazole in the blood and in the urine.

AUTHORS.

Bliss, C. I., and Allmark, M. G.: Digitalis Cat Assay in Relation to Rate of Injection. J. Pharmacol. & Exper. Therap. **81**: 378, 1944.

In the assay for digitalis the U. S. P. XII calls for adjusting the concentration of the injection fluid so that it will contain the estimated fatal dose per kilogram in 15 cubic centimeters. This is injected at the rate of 1 c.c. per kilogram every five minutes, and the average number of injections in an acceptable group of cats must not exceed limits of thirteen to nineteen for an official assay. To test the importance of this restriction, four groups, each of twelve cats, have been injected with dilutions containing 64, 80, 100, and 125 per cent, respectively, of the estimated fatal dose, in each case at the rate of 1 c.c. per kilogram. The experiment has been made with three different preparations of digitalis, requiring a total of one hundred forty-four cats.

In three experiments the lethal dose increased with the concentration of digitalis in the injection fluid which, in turn, controlled the rate of injection. The increase was statistically significant in two of the three cases. The relation between log-dose and log-concentration was linear and has been fitted by a straight line with an average slope of $b = 0.20 = 0.05$. In other words, a twofold increase in the concentration of tincture in the injection fluid increased the lethal dose in terms of the original tincture by approximately 15 per cent, apart from any other change in procedure. If the groups of cats comprising an assay were to require thirteen and nineteen injections, respectively, the greatest allowable difference, the percentage potency of the sample could be biased by 8 per cent through this factor alone. Since the relation between log-concentration and log-dose in these experiments is linear, the required concentration of the dilute solution could be decreased to the present minimum and yet not eliminate this factor. The potential bias could be reduced, however, by restricting the allowable difference in the average number of injections between the two groups of a single assay.

An alternative procedure for the cat assay has been examined with the present data, based upon the linear relation between log-concentration of the injection fluid and the log-minutes' survival time. In design and analysis it is equivalent to an assay based upon a graded response. The methods of statistical analysis suitable for self-contained assays have been extended, so that past experience can be used as it accumulates. When the present experiments were computed as test assays by this procedure, the estimated potencies agreed very well with the true value. The main advantage of the new technique is that it does not require as accurate a forecast of the potency of an unknown preparation as the official assay; its main disadvantage is that it would not reduce the number of cats needed to obtain a given precision. It should be of value, however, in the preliminary experiments which usually precede an official assay.

AUTHORS.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

DR. ROY W. SCOTT
President

DR. HOWARD F. WEST
Vice-President

DR. GEORGE R. HERRMANN
Treasurer

DR. HOWARD B. SPRAGUE
Secretary

BOARD OF DIRECTORS

*DR. EDGAR V. ALLEN	Rochester, Minn.†
DR. ARLIE R. BARNES	Rochester, Minn.
DR. WILLIAM H. BUNN	Youngstown, Ohio
DR. CLARENCE de la CHAPELLE	New York City
DR. NORMAN E. FREEMAN	Philadelphia†
*DR. TINSLEY R. HARRISON	Dallas
DR. GEORGE R. HERRMANN	Galveston
DR. T. DUCKETT JONES	Boston
DR. LOUIS N. KATZ	Chicago
*DR. SAMUEL A. LEVINE	Boston
DR. GILBERT MARQUARDT	Chicago†
*DR. H. M. MARVIN	New Haven
*DR. EDWIN P. MAYNARD, JR.	Brooklyn
*DR. THOMAS M. McMILLAN	Philadelphia
DR. JONATHAN MEAKINS	Montreal†
DR. E. STERLING NICHOL	Miami
DR. HAROLD E. B. PARDEE	New York City
DR. WILLIAM B. PORTER	Richmond, Va.
*DR. JOHN J. SAMPSON	San Francisco†
*DR. ROY W. SCOTT	Cleveland
DR. FRED M. SMITH	Iowa City
DR. HOWARD B. SPRAGUE	Boston†
DR. GEORGE F. STRONG	Vancouver, B.C., Can.
DR. WILLIAM D. STROUD	Philadelphia
DR. WILLIAM P. THOMPSON	Los Angeles
DR. HARRY E. UNGERLEIDER	New York City
*DR. HOWARD F. WEST	Los Angeles
DR. PAUL D. WHITE	Boston
DR. FRANK N. WILSON	Ann Arbor
*DR. IRVING S. WRIGHT	New York City†
DR. WALLACE M. YATER	Washington, D. C.

*EXECUTIVE COMMITTEE
†IN MILITARY SERVICE

DR. H. M. MARVIN, *Acting Executive Secretary*
ANNA S. WRIGHT, *Office Secretary*
TELEPHONE, CIRCLE 5-8000

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is $5.00. Journal membership at $11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is $10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.